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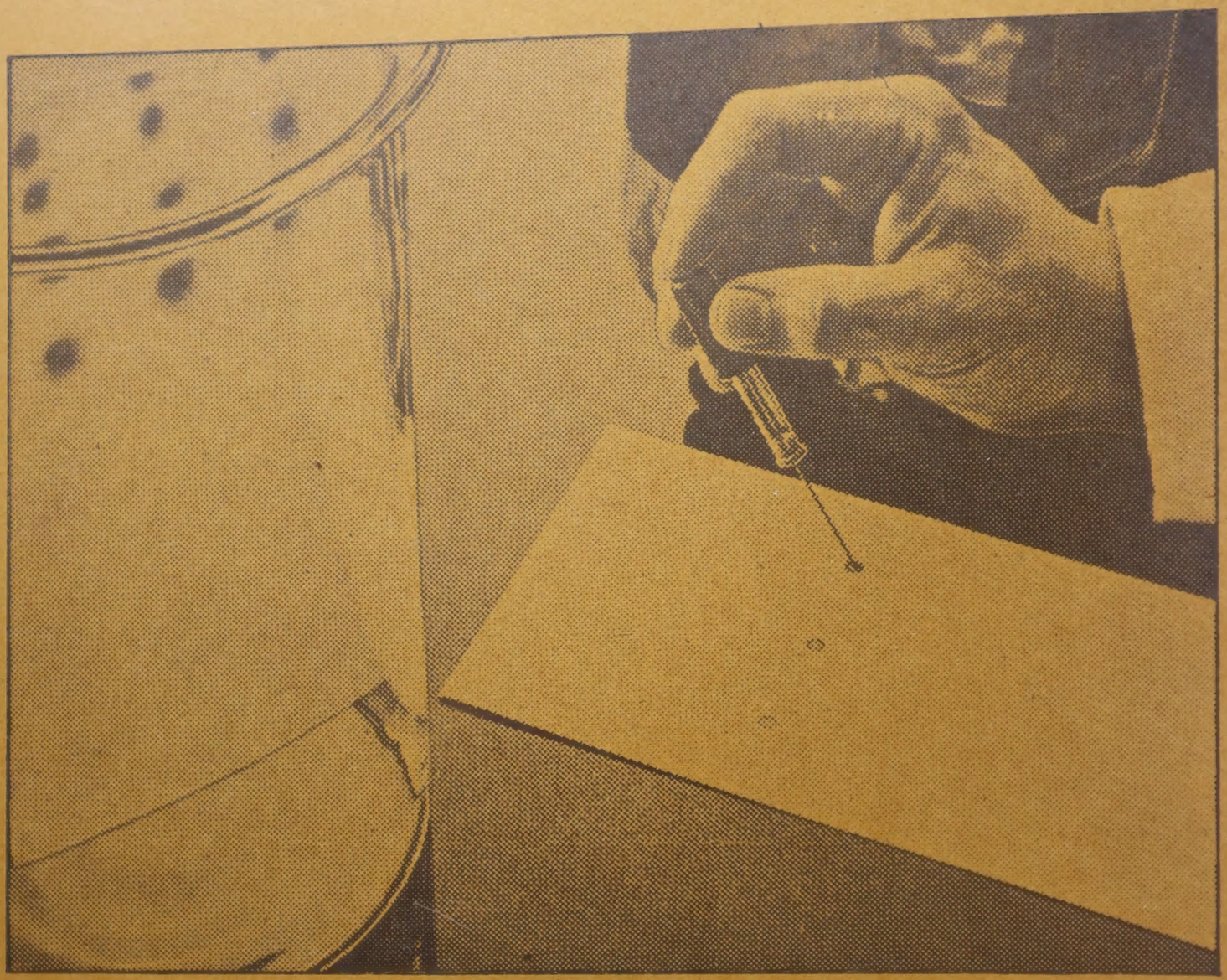

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Reaction of Dimedone with α-Keto Acids†

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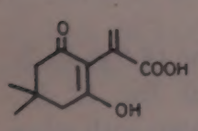
Received 2 *September* 1985; *accepted* 22 *October* 1985

The reaction of dimedone with pyruvic acid gives, in addition to the reported acid (**1**), the xanthene (**2a**). **2a** reacts with ammonium acetate to give **5a** and with aniline **5b**. With *n*-butylamine and isobutylamine, **2a** gives **6a** and **6b** respectively. Dimedone reacts with phenylglyoxylic acid to give **2f**, **7** and **9** and with 2-oxoglutaric acid **2h** and **10**.

The reaction of dimedone with pyruvic acid is reported to give the acrylic acid (**1**)[1,2]. In connection with the reaction of dimedone enamines with α-keto acids[3], we had an occasion to repeat the reaction. Whereas with excess of pyruvic acid (>2 mol per mol of dimedone) **1** is formed, when only 0.5 mol of pyruvic acid is used per mol of dimedone, a new acid (**2a**) is obtained.

The acid (**2a**) shows ν_{max} at 1720, 1660 cm^{-1} in nujol mull and at 1770 cm^{-1} in methylene chloride or dioxane solution, indicating that it is a dimer in solid and a monomer in solution[4]. Its PMR spectrum displays C_9-CH_3 as a singlet at δ 1.3, C_2- and C_7-Hs as a singlet (4H) at 2.2, C_4- and C_5-Hs as a singlet (4H) at 2.45 and the CH_3 groups on C-3 and C-6 as a singlet (12H) at 1.0. The isomeric alternate structures (**3**) and (**4a**) were considered because of the high ν_{max} in solution but ruled out by the ^{13}C NMR which showed the equivalence of rings A and C, viz. C-1 and C-8, C-2 and C-7, C-3 and C-6, C-4 and C-5, C-10 and C-13, and C-11 and C-12. The carbons of CH_3 groups on C-3 and C-6 appear as two signals in the ^{13}C NMR spectrum.



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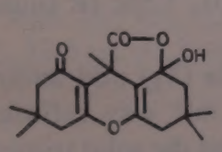

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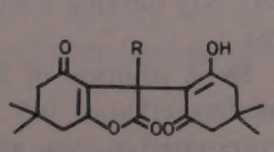
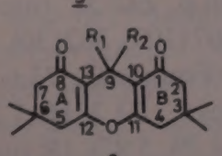


4a R = CH_3
4b R = H



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	R_1	R_2
2a	CH_3	COOH
2b	CH_3	$COOCH_3$
2c	CH_3	CH_3
2d	COOH	H
2e	CH_3	H
2f	phenyl	H
2g	phenyl	COOH
2h	COOH	CH_2CH_2COOH

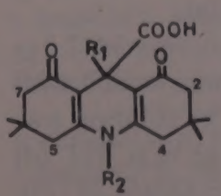
Treatment of the acid with diazomethane gives the ester (**2b**) whose ^1H and ^{13}C NMR spectra again show the equivalence of rings A and C.

Although the reaction of dimedone with aldehydes is a standard method of characterising aldehydes, the reaction of dimedone with ketones is not well-known. Acetone reacts with dimedone only under forcing conditions[5] (sealed tube, 40 hr) to give **2c**. In pyruvic acid, the α-ketoacid confers reactivity to the carbonyl group.

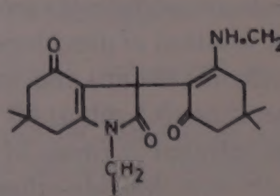
For comparison of spectra, the known compounds (**2d**)[6] and (**2e**)[5] were prepared. **2d** shows ν_{max} at 1725 cm^{-1} in nujol mull and 1765 cm^{-1} in methylene chloride. The ^1H and ^{13}C NMR spectra of **2a** and **2d** are similar. Both the compounds are recovered when treated with acetic anhydride, rulling out the structures (**4a**) and (**4b**) which contain an acylable dimedone unit.

Reaction of **2a** with ammonium acetate results in the formation of the acridine (**5a**). With aniline, **2a** gives **5b** in which C_4- and C_5-Hs are shielded by the phenyl group and appear as an *AB* quartet centred at δ 1.9. The C_2- and C_7-Hs appear as a singlet (4H) at 2.2. The ^1H and ^{13}C NMR spectra of **5b** are similar to those of **5c**[3].

Reaction of **2a** with *n*-butyl amine or isobutyl amine took a different turn and yielded **6a** and **6b** respectively. The molecular formula $C_{27}H_{42}N_2O_3$ in both cases (M^+ 442) showed the incorporation of two

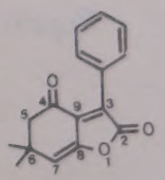


	R_1	R_2
5a	CH_3	H
5b	CH_3	phenyl
5c	H	phenyl



6a R = $CH_2.CH_2.CH_3$
6b R = $CH(CH_3)_2$

†Communication No. 780 from HINDUSTAN CIBA-GEIGY Research Centre, Bombay 400 063.



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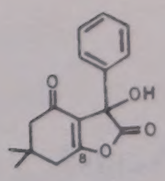

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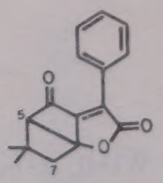

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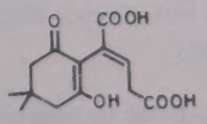

10

butyl amine molecules. The ^1H and ^{13}C NMR spectra of **6a** and **6b** showed the presence of two unsymmetrical dimedone units.

The reaction of phenylglyoxylic acid with dimedone results in three compounds one of which has been identified as the known **2f**[7]. This is evidently formed by decarboxylation of the expected **2g**. The second compound is assigned structure (**7**) and is formed by dehydration of the initially formed hydroxylactone (**8**). The latter, however, is not isolated. The third compound is isomeric with **7**, the significant differences being in the UV and PMR spectra. Whereas **7** shows C_7-H as a singlet at δ 6.0, C_5-H as a singlet at 2.7 and the CH_3 groups on C-6 as a singlet (6H) at 1.3, in **9** the C_5-H appears as a singlet at δ 2.7, C_7-H as an *AB* quartet at 2.39 and 3.14 (J = 18 Hz) and the CH_3 groups as two separate singlets at 1.1 and 1.0. **9** can arise from **8** by the addition of the carbanion next to the carbonyl group to C-8.

The reaction of 2-oxoglutaric acid with dimedone gives in poor yield two compounds (**2h**) and (**10**).

Experimental Procedure

M.ps. are uncorrected. UV spectra were taken in ethanol. IR spectra were taken on a Perkin-Elmer 684 spectrophotometer and NMR spectra on a Bruker WH-90 instrument, ^1H NMR at 90 MHz and ^{13}C NMR at 22.63 MHz. Mass spectra were taken on a Varian Mat CH-7 spectrometer by direct inlet system at 70 eV.

1,2,3,4,5,6,7,8-*Octahydro*-3,3,6,6,9-*pentamethyl*-1,8-*dioxoxanthene*-9-*carboxylic acid* (**2a**)

A solution of dimedone (7 g) and pyruvic acid (2.5 g) in ethanol (50 ml) and water (10 ml) was heated with piperidine (0.5 ml) at 80° for 12 hr. The solution was concentrated *in vacuo* to yield **2a** (3.1 g); m.p. 313° (d) (methylene chloride-ethanol); mass: m/z 332 (5), 317 (5), 288 (90), 287 (100), 273 (80), 272 (70), 232 (40) (Found: C, 68.3; H, 7.7. $C_{19}H_{24}O_5$ requires C, 68.7; H, 7.3%); UV: 229, 297 nm (log ε 4.21, 3.64); IR (nujol): 1720, 1660, 1620 cm^{-1}; IR (CH_2Cl_2): 1770, 1730, 1695, 1620 cm^{-1}; IR (dioxane): 1775, 1695, 1620 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.45 (4H, *s*), 2.2 (4H, *s*), 1.3 (3H, *s*), 1.0 (12H, *s*); ^{13}C NMR (DMSO-d_6): δ 195.6 (*s*), 172.8 (*s*), 161.7 (*s*), 116.0 (*s*), 50.9 (*t*), 40.1 (*t*), 39.0 (*s*), 31.3 (*s*), 27.5 (*q*), 27.0 (*q*), 23.2 (*q*); ester (**2b**) (ethereal diazomethane), m.p. 185° (ether-hexane); mass: m/z 346 (1), 331 (5), 303 (20), 289 (25), 288 (70), 287 (100), 231 (50) (Found: C, 69.1; H, 7.8. $C_{20}H_{26}O_5$ requires C, 69.3; H, 7.6%); IR (nujol): 1730, 1680, 1670 cm^{-1}; IR (CH_2Cl_2): 1770, 1735, 1680, 1630 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.7 (3H, *s*), 2.4 (4H, *s*), 2.25 (4H, *s*), 1.45 (3H, *s*), 1.1 (12H, *s*); ^{13}C NMR ($CDCl_3$): δ 195.9 (*s*), 174.4 (*s*), 162.1 (*s*), 117.2 (*s*), 52.1 (*q*), 51.4 (*t*), 41.2 (*t*), 39.9 (*s*), 31.8 (*s*), 28.7 (*q*), 27.4 (*q*), 23.8 (*q*).

2d[6]: m.p. 238-40° (ethanol), M^+ 318, IR (nujol): 1725, 1700, 1680, 1660, 1620 cm^{-1}; IR (CH_2Cl_2): 1765, 1685, 1670 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 4.3 (1H, *s*), 2.5 (4H, *s*), 2.3 (4H, *s*), 1.1 (12H, *s*); ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 194.1 (*s*), 170.5 (*s*), 162.3 (*s*), 109.5 (*s*), 48.9 (*t*), 39.3 (*t*), 30.8 (*d*), 30.4 (*s*), 27.4 (*q*), 25.2 (*q*).

2e[5]: m.p. 174° (ethanol), M^+ 288, IR (nujol): 1655, 1610 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.6 (1H, *q*), 2.35 (4H, *s*), 2.25 (4H, *s*), 1.1 (12H, *s*), 1.1 (3H, *d*).

1,2,3,4,5,6,7,8,9,10-*Decahydro*-3,3,6,6,9-*pentamethyl*-1,8-*dioxoacridine*-9-*carboxylic acid* (**5a**)

A mixture of **2a** (2.4 g) and powdered ammonium acetate (20 g) in acetic acid (40 ml) was refluxed for 16 hr and the solid filtered to yield **5a** (0.5 g); m.p. > 360° (acetic acid); mass: m/z 286 (80), 285 (75), 270 (35), 257 (40), 229 (100), 201 (35) (Found: C, 68.6; H, 7.3; N, 4.6. $C_{19}H_{25}NO_4$ requires C, 68.9; H, 7.6; N, 4.2%); UV: 247, 375 nm (log ε 4.01, 3.50); IR (nujol): 1725, 1645 cm^{-1}.

5b: A solution of **2a** (3 g) and aniline (4.5 g) in 2-methoxyethanol (45 ml) was refluxed for 12 hr, evaporated *in vacuo* and the solid triturated with ether to yield **5b** (1.5 g); m.p. 232-34° (methylene chloride-hexane); mass: m/z 407 (100), 362 (30), 323 (25), 268 (90), 252 (20), 212 (30) (Found: C, 73.6; H, 7.4; N, 3.8. $C_{25}H_{29}NO_4$ requires C, 73.7; H, 7.2; N, 3.4%); UV: 248, 373 nm (log ε 4.39, 3.97); IR (nujol): 1760, 1655, 1620 cm^{-1}; IR (CH_2Cl_2): 1760, 1730, 1655, 1635 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.0-7.7 (5H, *m*), 2.2 (4H, *s*), 1.9 (4H, *AB*, *q*), 1.6 (3H, *s*), 0.9 (12H, *s*); ^{13}C NMR ($CDCl_3$): δ 195.8 (*s*), 176.2 (*s*), 149.9 (*s*), 139.5 (*s*), 130.2 (*d*), 129.9 (*d*), 129.6 (*d*), 116.8 (*s*), 51.0 (*t*), 42.6 (*t*), 32.2 (*s*), 29.0 (*q*), 27.1 (*q*), 24.7 (*q*).

5c[3]: m.p. 230° (methylene chloride-hexane), UV: 252, 365 nm (log ε 4.30, 3.80); IR (nujol): 1765, 1650, 1595 cm^{-1}; IR (CH_2Cl_2): 1760, 1650, 1610 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.0-7.7 (5H, *m*), 4.9 (1H, *s*), 2.3 (4H, *s*), 1.9 (4H, *AB*, *q*), 1.0 (12H, *s*); ^{13}C NMR (DMSO-d_6): δ 194.6 (*s*), 172.8 (*s*), 151.4 (*s*), 138.3 (*s*), 129.8 (*d*), 129.4

(*d*), 129.2 (*d*), 108.9 (*s*), 49.6 (*t*), 40.8 (*t*), 32.1 (*d*), 31.7 (*s*), 29.1 (*q*), 25.7 (*q*).

Lactam (**6a**)

A solution of **2a** (5 g) and *n*-butyl amine (5 g) in ethanol (100 ml) was refluxed for 12 hr, evaporated *in vacuo* and the residue triturated with ether-hexane to yield **6a** (1.2 g); m.p. 177-79° (methylene chloride-hexane); mass: *m/z* 442 (40), 428 (25), 419 (35), 413 (28), 385 (25), 303 (50), 301 (100), 291 (45), 285 (50), 273 (45), 260 (45), 245 (50), 229 (40) (Found: C, 73.6; H, 9.8. $C_{27}H_{42}N_2O_3$ requires C, 73.3; H, 9.6%); UV: 287, 343 nm (log ε 4.41, 4.24), IR (nujol): 1750, 1650 cm^{-1}; IR (CH_2Cl_2): 1750, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.5 (2H, *q*), 3.4 (2H, *q*), 2.0-2.4 (8H, *m*), 1.65 (3H, *s*), 1.15 (12H, *s*), 0.93 (6H, *t*); ^{13}C NMR ($CDCl_3$): δ 191.2 (*s*), 190.0 (*s*), 183.5 (*s*), 164.2 (*s*), 163.1 (*s*), 114.9 (*s*), 109.8 (*s*), 51.1 (*t*), 50.2 (*t*), 46.3 (*s*), 44.8 (*t*), 41.0 (*t*), 39.3 (*t*), 36.1 (*t*), 33.5 (*s*), 31.5 (*s*), 31.1 (*q*), 28.7 (*q*), 28.3 (*q*), 20.8 (*d*), 20.1 (*q*), 13.6 (*q*).

Lactam (**6b**)

A solution of **2a** (5 g) and isobutyl amine (6 g) in *t*-butanol (30 ml) was refluxed for 16 hr and evaporated *in vacuo* to yield **6b** (1.5 g); m.p. 182-84° (methylene chloride-hexane); mass: *m/z* 442 (20), 427 (20), 399 (10), 385 (15), 302 (65), 287 (100), 259 (15), 246 (10), 231 (25) (Found: C, 72.9; H, 9.9. $C_{27}H_{42}N_2O_3$ requires C, 73.3; H, 9.6%); UV: 287, 345 nm (log ε 4.46, 4.26); IR (nujol): 1740, 1630, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.2-3.7 (4H, *m*), 1.9-2.6 (8H, *m*), 1.66 (3H, *s*), 1.1 (9H, *s*), 0.95 (12H, *d*, *J* = 6.5 Hz), 0.93 (3H, *s*); ^{13}C NMR ($CDCl_3$): δ 190.9 (*s*), 189.6 (*s*), 183.8 (*s*), 164.6 (*s*), 163.6 (*s*), 114.8 (*s*), 109.6 (*s*), 52.4 (*t*), 50.9 (*t*), 50.0 (*t*), 48.7 (*t*), 46.1 (*s*), 39.3 (*t*), 36.2 (*t*), 33.6 (*s*), 31.3 (*s*) (higher field signals crowded).

Reaction of dimedone with phenyl glyoxylic acid

A solution of dimedone (5.6 g) and phenyl glyoxylic acid (6.0 g) in 2-methoxy ethanol (50 ml) and water (10 ml) was refluxed with piperidine (0.5 ml) for 8 hr. The solution was evaporated *in vacuo* and the residue chromatographed over silica gel in methylene chloride, eluting with increasing amounts of methanol to yield the following three compounds:

(1) **7** (0.4 g); m.p. 117-18° (methylene chloride-methanol); mass: *m/z* 254 (60), 239 (100), 226 (10), 211 (25), 129 (70) (Found: C, 75.5; H, 5.7. $C_{16}H_{14}O_3$ requires C, 75.6; H, 5.6%); UV: 227, 350 nm (log ε 4.09, 4.25); IR (nujol): 1760, 1700, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.9-8.1 (2H, *m*), 7.4-7.5 (3H, *m*), 6.0 (1H, *s*), 2.7 (2H, *s*), 1.3 (6H, *s*); ^{13}C NMR ($CDCl_3$): δ 193.6 (*s*), 168.1 (*s*), 148.6 (*s*), 131.1 (*d*), 130.6 (*d*), 128.3 (*d*), 128.3 (*s*), 128.0 (*s*), 120.6 (*d*), 56.6 (*t*), 36.5 (*s*), 30.4 (*q*).

(2) **9** (0.2 g); m.p. 225-27° (methylene chloride-methanol); mass: *m/z* 254 (80), 239 (100), 226 (15), 211 (50), 129 (60) (Found: C, 75.6; H, 5.3. $C_{16}H_{14}O_3$ requires C, 75.6; H, 5.6%); UV: 313 nm (log ε 3.50); IR (nujol): 1785, 1770, 1765 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.8-7.9 (2H, *m*), 7.3-7.5 (3H, *m*), 3.14 (1H, *d*, *J* = 18 Hz), 2.7 (1H, *s*), 2.39 (1H, *d*, *J* = 18 Hz), 1.1 (3H, *s*), 1.0 (3H, *s*); ^{13}C NMR ($CDCl_3$): δ 191.4 (*s*), 168.8 (*s*), 145.8 (*s*), 134.3 (*s*), 131.5 (*d*), 131.3 (*d*), 127.9 (*d*), 127.2 (*s*), 89.3 (*s*), 50.3 (*t*), 48.8 (*d*), 33.9 (*s*), 28.2 (*q*), 26.2 (*q*).

(3) **2f** (0.2 g); m.p. 207-8° (Lit.[7] m.p. 193°), M$^+$ 350; UV: 234, 300 nm (log ε 4.17, 3.69); IR (KBr): 1680, 1660, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.1-7.3 (5H, *m*), 4.75 (1H, *s*), 2.46 (4H, *s*), 2.19 (4H, *s*), 1.09 (6H, *s*), 0.98 (6H, *s*).

Reaction of dimedone with 2-oxoglutaric acid

A solution of dimedone (5.5 g) and 2-oxoglutaric acid (6 g) in ethanol (100 ml) and water (10 ml) was refluxed with piperidine (1 ml) for 12 hr, evaporated *in vacuo* and the residue chromatographed over silica gel in methylene chloride, eluting with increasing amounts of methanol to yield the following two compounds:

(1) **2h** (0.1 g); m.p. 255-56° (acetone-ether); mass: *m/z* 390 (2), 345 (100), 329 (5), 317 (10), 299 (80), 286 (70), 273 (65), 217 (20) (Found: C, 64.1; H, 6.5. $C_{21}H_{26}O_7$ requires C, 64.6; H, 6.7%); UV: 230, 302 nm (log ε 4.24, 3.62); IR (nujol): 1720, 1660, 1635 cm^{-1}.

(2) **10** (0.1 g); m.p. 196-98° (acetone-ether); mass: *m/z* 268 (10), 250 (35), 206 (100), 178 (20), 165 (25) (Found: C, 58.0; H, 6.6. $C_{13}H_{16}O_6$ requires C, 58.2; H, 6.0%); UV: 261 nm (log ε 4.14); IR (nujol): 1710, 1680 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 6.8 (1H, *t*, *J* = 7 Hz), 2.9 (2H, *d*, *J* = 7 Hz), 2.2 (4H, *s*), 1.0 (6H, *s*); ^{13}C NMR (DMSO-d_6): δ 182.7 (*s*), 171.2 (*s*), 167.1 (*s*), 136.2 (*d*), 128.6 (*s*), 109.7 (*s*), 46.4 (*t*), 34.7 (*t*), 31.4 (*s*), 27.7 (*q*).

Note added in proof:

Compound **9** has been subjected to an X-ray investigation. The structure has to be revised to a cyclobutane-containing dimer of compound **7** (T N Guru Row and K Venkatesan, private communication).

Acknowledgement

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Reaction of Aldonitrones with Copper Acetylide : Synthesis of Some Novel β-Lactams

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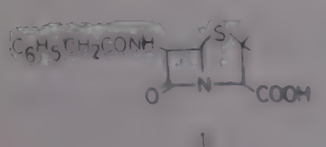
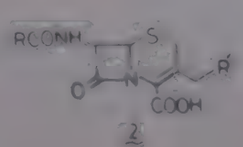
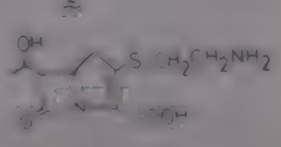
Nitrones (7a-e) react with copper acetylide (**6**) to afford *cis*- and *trans*-β-lactams (**8** and **9**) in good yields. The *cis*- and *trans*-isomers have been isolated, respectively as the major and minor products and are characterized through spectral data (IR, mass and PMR).

Since the discovery of penicillin-G (**1**), there has been tremendous effort to understand and further modify the basic unit as well as to carry on manipulations in the side chain of the parent molecule in order to obtain more selective and effective antibacterial agents[1,2]. These efforts resulted in the development of ampicillin, amoxicillin and a group of cephalosporins (**2**) as clinically selective and effective chemotherapeutic agents. Recently the discovery of monobactams[3] (**3**) and thienamycin[4] (**4**) group of unconventional chemotherapeutic agents have provided a new lead to the medicinal chemists. All the eight naturally occurring monobactams are isolable only in small quantities and are not suitable for any further semisynthetic modifications[5]. These chemical species are unconventional β-lactam antibiotics in the sense that they do not contain the basic unit available in the parent **1**. The synthesis of simple β-lactams have been purely of academic interest till the discovery of **3** and **4**; but these convenient synthetic routes leading to monobactams are now becoming of medicinal value[6]. The synthesis involving carbon-nitrogen double bond and ketenes (produced *in situ*) has been a facile route for the production of simple β-lactams[7]. Also imines when reacted with azlactones produce substituted β-lactam units[8]. Cycloaddition reactions of nitrones. with various multiple as well as hetero multiple bonds are well documented[9]. However, recent reinvestigations of the available procedures for β-lactams has brought out contradictions in these approaches[10].

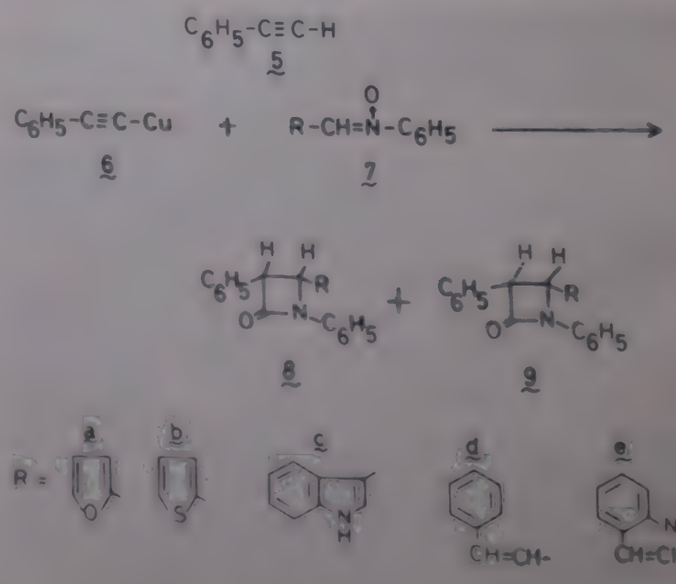






In these reinvestigations major efforts have been directed in the reactions of differently substituted acetylene with nitrones[11]. Herein we wish to describe the synthesis of some novel β-lactams by the reactions of a few aldonitrones with copper acetylide.

Copper acetylide (**6**) was prepared *in situ*, from phenylacetylene (**5**) and cuprous chloride in pyridine employing concentrated ammonia as a base. The substituted nitrones (**7a-e**) were prepared from phenylhydroxylamines and corresponding aldehydes[12]. The reactions of nitrones with copper acetylide were performed at room temperature using pyridine as a solvent. The reaction between furylidineaniline-N-oxide (**7a**) and **6** for 2 hr resulted in a TLC single product which on the basis of its IR, mass and PMR spectral data (Table 1) was assigned the structure as 1,3-diphenyl-4-furylazitidin-2-one (**8a**) (Scheme 1). That the **8a** has a *cis*- geometry was evident from the coupling-coupling constant of 6 Hz for H-3 and H-4 protons, a characteristic[13] of *cis*- β - lactams. But the reaction of thienylidineaniline-N-oxide (**7b**) with **6** under similar reaction condition afforded 1,3-



Scheme 1

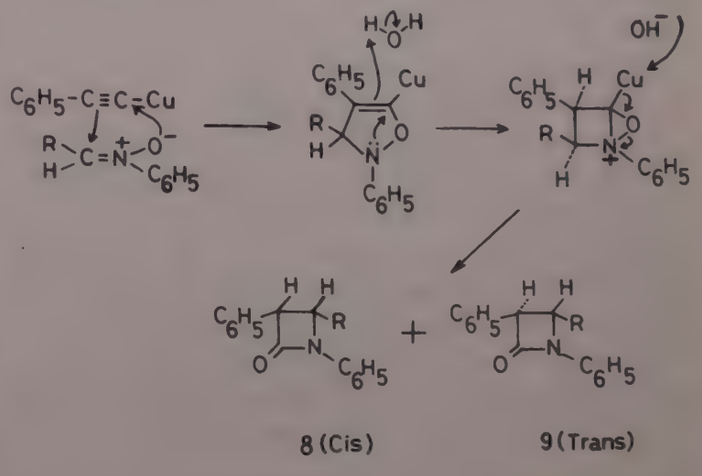
Table 1—IR, PMR and Mass Spectral Data of *cis*- and *trans*-azetidine-2-ones (**8** and **9**)

Compd	ν C=O (cm^{-1})	PMR (δ-scale)	Mass (m/z)
8a	1740	5.00 (1H, *d*), 5.40 (1H, *d*), 7.00-7.40 (13H, *m*), (*J*=6 Hz).	289, 171, 119, 118
8b	1740	4.85(1H,*d*), 5.55(1H,*d*), 7.00-7.40 (13H, *m*), (J=6 Hz)	305, 187 119, 118.
9b	1740	4.30 (1H, *d*), 5.15 (1H, *d*) 7.10-7.40 (13H, *m*), (*J*=2.5 Hz)	305, 187, 119, 118.
8c	1740	5.00 (1H, *d*), 5.70 (1H, *d*), 6.80-7.40 (16H, *m*), (*J*=6 Hz).	338, 220, 119, 118.
9c	1750	4.40 (1H, *d*), 5.25 (1H, *d*), 7.00-8.2 (16H, *m*), (*J*=2.5 Hz).	338, 220, 119, 118.
8d	1745	4.70 (1H, *d*), 5.55 (1H, *dd*), 6.00 (2H, *q*), 7.10-7.45 (15H, *m*), (*J*=6.2 Hz).	325, 207, 119, 118.
9d	1745	4.05 (1H, *d*), 4.95 (1H, *dd*), 6.05 (2H, *q*), 7.00-7.45 (15H, *m*), (*J*=2.5 Hz).	325, 207, 119, 118.
8e	1745	4.65 (1H, *d*), 5.60 (1H, *dd*), 5.95 (2H, *q*), 7.15-7.55 (14H, *m*), (*J*=6 Hz).	370, 252, 119, 118.

diphenyl-4-thienylazitidin-2-one as a mixture of two isomers which were separated through fractional crystallisation (Table 2). Both the isomers displayed IR absorption bands at 1740 cm^{-1} characteristic of β-lactam carbonyl. The mass spectra showed the molecular ion peak (M^+) at *m/z* 305 for both the isomers. The stereochemistry of the two isomers was finally resolved through PMR spectral data. The major product exhibited a multiplet at δ 7.00-7.40 for aromatic protons and two doublets of one-proton each at 5.55 and 4.85 (*J*=6 Hz). The PMR spectrum of the minor product exhibited the aromatic proton multiplet in the region δ 7.1-7.4 and two doublets of one-proton each at 5.15 and 4.30 with *J*=1.5 Hz. These observations are in confirmity with the reported observations that *trans*- β-lactam protons appear upfield with lower J values as compared to *cis*- β-lactam[13]. On the basis of this the major product was assigned the *cis*- geometry (**8b**) while the minor product the *trans*- geometry (**9b**).

Regarding the mechanism of this reaction it appears that the nitrone cycloadds to the acetylenic bond as a 1,3-dipole, followed by the attack of the unstable intermediate with a water molecule and loss of metallic copper as its hydroxide (Scheme 2).

Similarly **7d** reacted with copper acetylide (**6**) affording *cis*- and *trans*- isomers (**8d**) and (**9d**)



Scheme 2

Table 2—Characterisation Data of *cis*- and *trans*-azetidin-2-ones

Compd	m.p. (°C)	Yield (%)	Crystallised from	Mol. formula	Calc. (Found) % C	H	N
8a	168-70	55	Methanol	$C_{19}H_{15}NO_2$	78.9 (78.6	5.2 5.1	4.8 4.6)
8b	175-77	44	Ethanol	$C_{19}H_{15}NOS$	74.7 (74.6	5.0 4.8	4.6 4.5)
9b	157-58	11	Methanol	$C_{19}H_{15}NOS$	74.7 (74.6	5.0 4.9	4.6 4.5)
8c	195-96	40	Do	$C_{23}H_{18}N_2O$	81.6 (81.5	5.4 5.5	8.3 8.1)
9c	175-76	15	Ethanol	$C_{23}H_{18}N_2O$	81.6 (81.5	5.4 5.3	8.2 8.1)
8d	155-56	46	Chloroform methanol	$C_{23}H_{19}NO$	84.9 (84.8	5.9 6.0	4.3 4.2)
9d	100-101	10	Methanol	$C_{23}H_{19}NO$	84.9 (84.8	5.9 5.8	4.3 4.2)
8e	182-86	40	Do	$C_{23}H_{18}N_2O_3$	74.6 (74.4	4.9 4.6	7.6 7.4)

respectively as the major and minor products (Table 2). In case of this reaction of cinnamylidinaniline-N-oxide (**7d**) with **6**, the isolable reaction products were only β-lactam isomers. There was no evidence for the formation of any cycloadduct involving the conjugated double bond of nitrones (**7d**,**e**) and **6**. The reaction of *o*-nitrocinnamilidinaniline-N-oxide (**7e**) with **6** resulted in *cis*-1,3-diphenyl-4-(*o*-nitrostyryl)-azetidin-2-one as single isolable product, alongwith some uncharacterisable polymeric products.

Experimental Procedure

Melting points are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer spectrophotometer and PMR spectra in $CDCl_3$ on a Varian T-60 instrument, chemical shifts are reported in δ-scale downfield from internal TMS. Phenylhydroxylamine[14], indole-3-carboxaldehyde[15] and *o*-nitrocinnamaldehyde[16] were prepared according to reported procedures.

2-Furfurylideneaniline-N-oxide (**7a**) *and thienylidineaniline-N-oxide* (**7b**)

A mixture of furfural-2-aldehyde (0.1 mol) and phenylhydroxylamine (0.1 mol) was taken in dry ether (100 ml) and stirred at room temperature for 6 hr. The reaction mixture was cooled and the solid that precipitated out was filtered and recrystallized from *n*-hexane to afford **7a** in 95% yield, m.p. 89-91°.

Reaction of thiophene-2-aldehyde (0.1 mol) with phenylhydroxylamine under similar condition yielded **7b** in 92% yield, m.p. 98-100° (pet. ether).

3-Indolydineaniline-N-oxide (**7c**)

A mixture of indole-3-carboxaldehyde (0.1 mol) and phenylhydroxylamine was refluxed in benzene (100 ml) for 4 hr. The reaction mixture was concentrated to half of its volume and cooled. The solid that separated out was filtered and recrystallized from benzene-pet. ether, yield 89%, m.p. 172-74°.

Cinnamylidineaniline-N-oxide (**7d**)

The reaction of cinnamaldehyde (0.1 mol) with phenylhydroxylamine (0.1 mol) in water (100 ml) at room temperature afforded **7d** in 93% yield, m.p. 150-52° (from benzene-pet. ether).

o-Nitrocinnamylidineaniline-N-oxide (**7e**)

The reaction of *o*-nitrocinnamaldehyde (0.1 mol) with phenylhydroxylamine (0.1 mol) in ethanol (100 ml) at reflux for 1 hr afforded **7e** in 90% yield, m.p. 184-86° (from methanol).

General procedure for reaction of **7** *with copper acetylide* (**6**)

A mixture of nitrone (0.05 mol) and phenylacetylene (0.05 mol) was taken in pyridine (20 ml) and stirred. To this was added a mixture of cuprous chloride in conc ammonia (2 ml) and stirred at room temperature for 2 hr. The reaction mixture was poured into dil HCl (50 ml, 50%) and heated on a water-bath for 30 min, extracted with chloroform, the organic extract washed with saturated aq sodium bicarbonate and dried (anhyd Na_2CO_3). Removal of solvent yielded a white compound which was subjected either to fractional crystallisation or to column chromatography employing different solvent systems as eluents.

Reaction of **6** *with furfurylidineaniline-N-oxide* (**7a**)

TLC indicated the formation of one product (**8a**).

Reaction with thinylidineaniline-N-oxide (**7b**)

Fractional crystallization of the product from ethanol afforded *cis*- **8b** as white crystals. The mother liquor was evaporated to dryness and the residue recrystallised from methanol to afford the *trans*-isomer (**9b**).

Reaction with 3-indolylidineaniline-N-oxide (**7c**)

The product was chromatographed over silica gel using benzene as eluent to obtain *cis*-1,3-diphenyl-3-indolyl-azetidin-2-one (**8c**). Subsequent elution of the column with dichloromethane and work up gave the *trans*-1,3-diphenyl-3-indolyl-azetidine-2-one (**9c**) in 15% yield.

Reaction with cinnamylidinaniline-N-oxide (**7d**)

The product was chromatographed over silica gel eluting with benzene to obtain *cis*-1,3-diphenyl-4-styryl-azetidin-2-one (**8d**) as the major product and *trans*-1,3-diphenyl-4-styryl-azetidin-2-one (**9d**) as the minor product (10%).

Reaction with o-nitrocinnamalidinaniline-N-oxide (**7e**)

The product was chromatographed over silica gel using benzene as eluent to obtain only *cis*-1,3-diphenyl-4-(*o*-nitrostyryl)-axetidin-2-one (**8e**). Characterisation data of the various β-lactams obtained are given in Table 2.

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Heterocyclic Systems Containing Bridgehead Nitrogen Atom: Part LIII—Facile Synthesis of Spiro[cyclododecane-1,3′(4′*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine], a Novel & New Heterocyclic System

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6′(7′*H*)-Oxospiro[cyclododecane-1,3′(4′*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine] (III) and 6′-arylspiro[cyclododecane-1,3′(4′*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine]hydrobromides (IVa-d) have been synthesized by the reaction of 13,14,16,17-tetraazaspiro[5.11]heptadecane-15-thione (II) with chloroacetic acid and α-halogenoketones, respectively. 7-Arylidene-6′(7′*H*)-oxospiro[cycloheptane-1,3′(4′*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazines] (Va-d) have been prepared by the condensation of III with aldehydes. Compounds III-V represent a novel and hitherto unknown heterocyclic system. The structures III-V have been established by their IR, PMR and mass spectral data.

As a part of our research programme on the synthesis of novel and unknown bridgehead nitrogen heterocyclic systems, we have reported earlier the syntheses of thiazolobenzotriazines[1], dibenzodiazepinothiazoloquinoxaline[2], quinolinothiazolobenzimidazole[2], thiazolotriazinoindoles[3], triazolothiazoloquinoxaline[4], thiazolotriazolothiadiazine[5], thiazolodiazepine[6], thiazoloperimidine[7], spiro[cyclohexane-thiazolotetrazine][8] and spiro[cyclopentane-thiazolotetrazine][9] ring systems. We now wish to report the synthesis of spiro[cyclododecane-thiazolotetrazine], another novel and hitherto unknown bridgehead nitrogen heterocyclic system.

Cyclododecanone (I) on condensation with thiocarbohydrazide following the method of Lamon[10] for the synthesis of 6,7,9,10-tetraazaspiro[4.5]decane-8-thione, gave 13,14,16,17-tetraazaspiro[5.11]heptadecane-15-thione (II) which on reaction with chloroacetic acid and α-halogenoketones resulted in the facile syntheses of 6′(7′*H*)oxospiro[cyclododecane-1,3′(4′*H*)-[2*H*]thiazolo-[3,2-*b*]-*s*-tetrazine] (III) and 6′-arylspiro[cyclododecane-1,3′(4′*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine] hydrobromides (IVa-d), respectively (Scheme 1). The 7′-arylidenethiazolidinones (Va-d) were prepared by the condensation of III with aromatic aldehydes. The structures of thiazolidinone (III), arylidenethiazolidinones (V) and thiazoles (IV) were established by their spectral data. The parent thiazolidinone (III) absorbed at 1730 cm^{-1} ($\geq N-\overset{O}{\overset{\|}{C}}-$), but the unsaturation at 7′-position being conjugated with the carbonyl group at 6′-position as in the case of arylidenethiazolidinones (Va-d) showed a bathochromic shift[11]. The carbonyl absorption bands appeared at 1680, 1700, 1690 and 1700 cm^{-1} in the IR spectra of Va-d, respectively. The appearance of a multiplet centered at δ 1.59 integrating for eighteen protons (3-, 4-, 5-, 6-, 7-, 8-, 9-, 10- and 11-CH_2 of cyclododecane moiety), of Va-d, respectively. The appearance of a multiplet centered at δ 1.59 integrating for eighteen protons (3-, 4-, 5-, 6-, 7-, 8-, 9-, 10- and 11-CH_2 of cyclododecane moiety), a triplet at 3.04 integrating for four protons (2- and 12-CH_2 of cyclododecane moiety) and a singlet at 4.30 due to SCH_2 protons in the PMR spectrum and the exhibition of molecular ion peak at *m/z* 310 in the mass spectrum of the compound obtained from II and chloroacetic acid are consistent with the proposed structure (III).

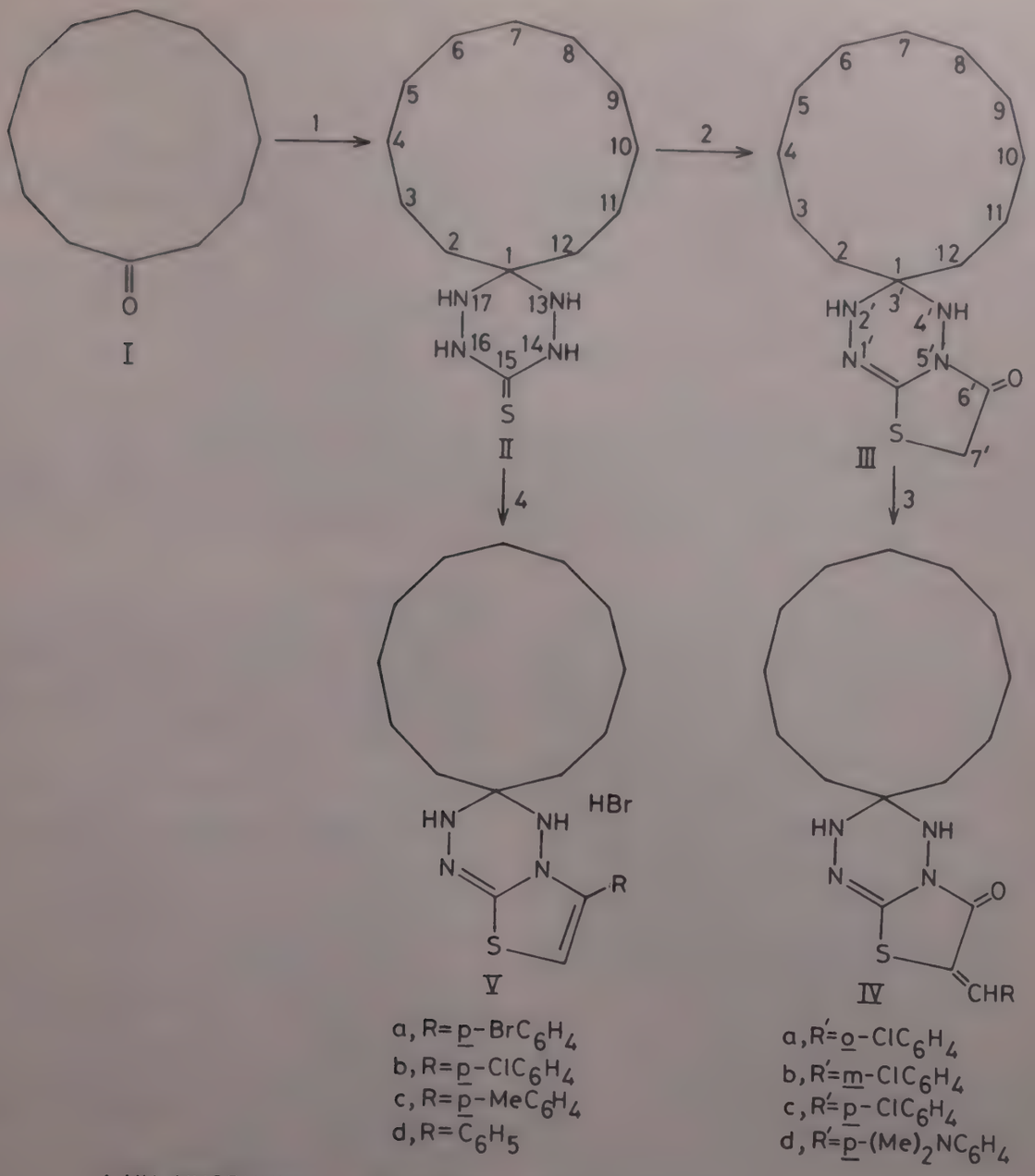
Lack of carbonyl absorption in the region 1660-1700 cm^{-1} in the IR spectra and the appearance of a signal at δ 6.91-6.99 due to C_7-H proton in the PMR spectra of the products obtained by the reaction of II with α-halogenoketones confirmed that the cyclization had indeed taken place, and in turn were in agreement with the assigned structure IV.

Experimental Procedure

Melting points are uncorrected. TLC was performed on silica gel plates using benzene-acetone (3:1) as irrigant. IR spectra were recorded in nujol mull on a Beckman IR-20 spectrophotometer (ν_{max} in cm^{-1}) and PMR spectra in TFA on a Perkin-Elmer 90 MHz spectrometer using TMS as internal standard (chemical shifts in δ, ppm). Mass spectrum was scanned on a Perkin-Elmer-Hitachi RMU-6D instrument at 70 eV.

13,14,16,17-*Tetraazaspiro*[5.11]*heptadecane-15-thione* (*II*)

To a solution of thiocarbohydrazide (10.6 g, 0.1 mol) in hot water (200 ml), cyclododecanone (I, 18.2 g, 0.1



1. $NH_2NHCSNHNH_2$; 2. $ClCH_2CO_2H$, NaOAc anhydrous;
3. R'CHO, NaOAc anhydrous; 4. $RCOCH_2Br$

Scheme 1

mol) in ethanol (30 ml) was added dropwise under stirring. The product began to precipitate during the course of addition. The reaction mixture was kept overnight at room temperature. The resultant white solid was filtered, washed well with dilute alcohol and air-dried, m.p. 60°, yield 20 g (74%) (Found: S, 11.6. $C_{13}H_{26}N_4S$ requires S, 11.9%); IR: 1585 (C=N), 3160 (NH).

6'(7'H)-Oxospiro[cyclododecane-1,3'(4'H)-[2H]thiazolo[3,2-b]-s-tetrazine] (III)

A mixture of II (2.7 g, 0.01 mol), chloroacetic acid (0.94 g, 0.01 mol) and anhyd. sodium acetate (0.82 g, 0.01 mol) in anhyd. ethanol (50 ml) was heated under reflux for 2 hr and cooled to room temperature. The solid, thus separated, was filtered, washed well with water and crystallized from ethanol as white flakes, m.p. 153°, yield 1.8 g (58%) (Found: C, 58.7; H, 8.3; S, 10.2; N, 18.0; M^+ at *m/z* 310. $C_{15}H_{26}N_4SO$ requires C, 58.6; H, 8.4; S, 10.3; N, 18.1%; Mol. wt 310); IR: 1590, 1620 (C=N, C=C), 1730 (C=O), 3200-3300 (NH); PMR: 1.59 (18H, *m*, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10- and 11-CH_2 of cyclododecane moiety), 3.04 (4H, *t*, 2- and 12-CH_2 of cyclododecane moiety), 4.30 (2H, *s*, SCH_2).

6'-(p-Bromophenylspiro[cyclododecane-1,3'(4'H)-[2H]thiazolo-[3,2-b]-s-tetrazine]-hydrobromide (IVa)

A mixture of II (2.70 g, 0.01 mol) and *p*-bromophenacyl bromide (2.78 g, 0.01 mol) in anhyd. ethanol (40 ml) was heated under reflux for 5 min and

cooled to room temperature. The solid, thus separated, was filtered, washed well with water and crystallized from ethanol to give TLC-pure IVa as white needles, m.p. 185°, yield 2.3 g (43%) (Found: C, 47.2; H, 5.6; S, 6.0; N, 10.6. $C_{21}H_{30}N_4Br_2S$ requires C, 47.6; H, 5.7; S, 6.0; N, 10.6%); IR: 1590 (C=N), 3020, 3080 (NH); PMR: 1.67 (18H, *m*, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10- and 11-CH_2 of cyclododecane moiety), 2.8 (4H, *m*, 2- and 12-CH_2 of cyclododecane moiety), 6.97 (1H, *s*, C_7–H), 7.61 (4H, AB_q Ar–*H*, J_{AB}=9 Hz).

In a similar way compounds IVb-d were prepared. Their characterization data are as follows:

IVb: m.p. 195°, yield 42% (Found: S, 6.4. $C_{21}H_{30}N_4BrClS$ requires S, 6.6%); IR: 1620 (C=N), 3100-3220 (NH); PMR: 1.64 (18H, *m*, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10- and 11-CH_2 of cyclododecane moiety), 2.80 (4H, *m*, 2- and 12-CH_2 of cyclododecane moiety), 6.97 (1H, *s*, C_7–H), 7.51 (4H, *m*, Ar–*H*).

IVc: m.p. 185°, yield 44% (Found: S, 6.8. $C_{22}H_{33}N_4SBr$ requires S, 6.9%); IR: 1600 (C=N), 3220 (NH); PMR: 1.64 (18H, *m*, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10- and 11-CH_2 of cyclododecane moiety), 2.44 (3H, *s*, CH_3), 2.83 (4H, *m*, 2- and 12-CH_2 of cyclododecane moiety), 6.91 (1H, *s*, C_7–H), 7.41 (4H, *m*, Ar–*H*).

IVd: m.p. 180°, yield 49% (Found: S, 7.0. $C_{21}H_{31}N_4SBr$ requires S, 7.1%); IR: 1600 (C=N), 3100 (NH); PMR: 1.64 (18H, *m*, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10- and 11-CH_2 of cyclododecane moiety), 2.82 (4H, *m*, 2- and 12-CH_2 of cyclododecane moiety), 6.99 (1H, *s*, C_7–H), 7.57 (5H, *m*, Ar–*H*).

7′-(o-Chlorobenzylidene)-6′(7′H)-oxospiro-[cyclododecane-1,3′(4′H)-[2H]thiazolo-[3,2-b]-s-tetrazine] (Va)

A mixture of III (0.775 g, 0.0025 mol), *o*-chlorobenzaldehyde (0.351 g, 0.0025 mol) and anhyd. sodium acetate (0.205 g, 0.0025 mol) in gl. acetic acid (8 ml) was heated under reflux for 3 hr and kept overnight at room temperature. The solid, thus separated, was filtered, washed well with water and crystallized from gl. acetic acid to give Va as yellow flakes, m.p. 205°, yield 0.3 g (28%) (Found: S, 7.2. $C_{22}H_{29}N_4SOCl$ requires S, 7.4%); IR: 1610 (C=N), 1690 (C=O), 3160 (NH).

Following compounds of the type V were also prepared in a similar manner. Their characterization data are as follows:

Vb: m.p. 225°, yield 36% (Found: S, 7.2. $C_{22}H_{29}N_4SOCl$ requires S, 7.4%); IR: 1620 (C=N), 1700 (C=O), 3140 (NH).

Vc: m.p. 200°, yield 43% (Found: S, 7.2. $C_{22}H_{29}N_4SOCl$ requires S, 7.4%); IR: 1620 (C=N), 1700 (C=O), 3140 (NH).

Vd: m.p. 170°, yield 44% (Found: S, 7.3. $C_{24}H_{35}N_5SO$ requires S, 7.5%); IR: 1620 (C=N), 1700 (C=O), 3100-3220 (NH).

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Reaction of N,N-Dimethyl-N′-thiobenzoylformamidine & N,N-Dimethyl-N′-phenylthiocarbamoylformamidine with N-Arylbenzimidoyl Chlorides

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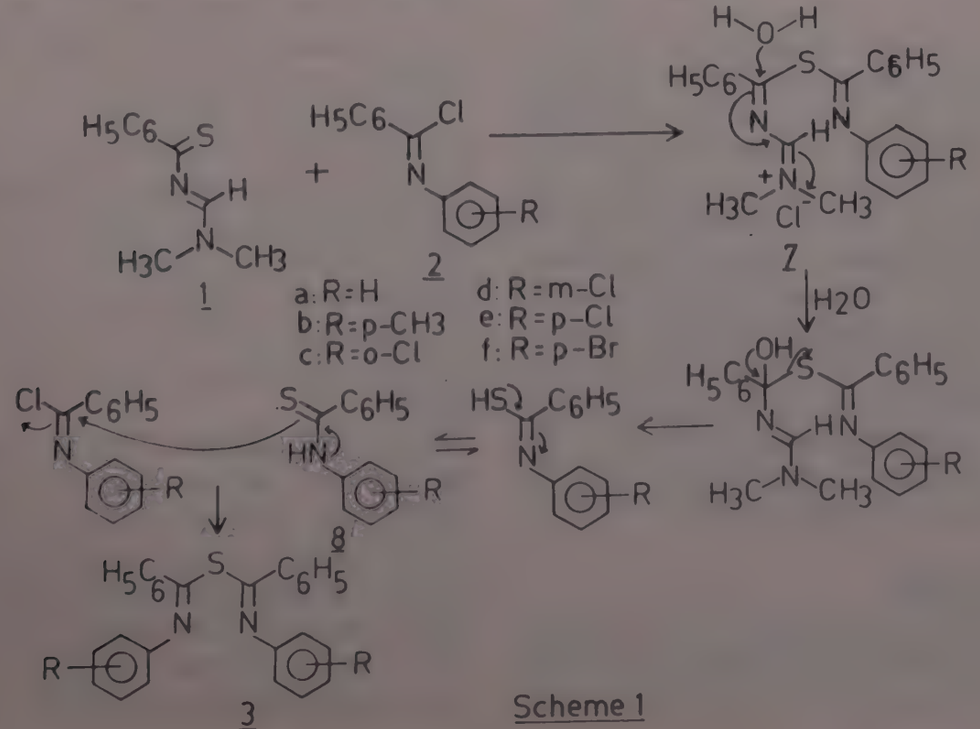
The reactions of N,N-dimethyl-N′-thiobenzoylformamidine (**1**) and N,N-dimethyl-N′-phenylthiocarbamoylformamidine (**4**) with N-arylbenzimidoyl chlorides (**2**) have been studied. Compound **1** reacts with **2** in dry chloroform at room temperature to give dimidoyl sulphides (**3**) in good yields. However, the reaction of **2** with **4** in dry tetrahydrofuran under reflux results in the formation of a mixture of thiobenzanilides (**5**) and N-aryl-N′-phenylbenzamidines (**6**). Possible mechanistic pathways for these reactions have been suggested.

Recently a number of reports have appeared in literature[1-4] describing the synthesis of a variety of heterocycles from N,N-dialkyl-N′-thioaroylformamidines (**1**) and α,β-unsaturated substrates such as ketenes and sulphanes, through (4+2) cycloaddition reaction. Eventhough all carbon dienes[5] are reported to undergo (4+2) cycloaddition with substrates having a carbon nitrogen double bond, for example imidoyl chlorides, there have been no reports in literature on the reactions of **1** with substrates having a carbon nitrogen double bond.

We have now explored the reactions of the heterodienes **1** and **4** with N-arylbenzimidoyl chlorides (**2**) in order to study the reaction pathways followed and the nature of the products formed in these cases. Thus, N,N-dimethyl-N′-thiobenzoylformamidine (**1**) reacted with **2** in dry chloroform, affording the dimidoylsulphides in good yields. The formation of **3** in this cases could be rationalised by the mechanistic pathways shown in Scheme 1. It has been presumed that **1** initially reacts with imidoyl chloride (**2**) to give an immonium salt (**7**) which reacts with water with the formation of a thiobenzanilide (**8**), which in turn reacts with another molecule of **2** to give **3**. The structures of the dimidoylsulphides (**3**) were established on the basis of their analytical and spectral data (Table 1).

The reaction of N,N-dimethyl-N′-phenylthiocarbamoylformamidine (**4**), where the nonbonding electron pair at nitrogen attached to phenyl can also polarise the thiocarbonyl group, with N-phenylbenzimidoyl chloride (**2a**) in refluxing dry THF gave a mixture of products consisting of N,N′-diphenylbenzamidine (**6a**; 33%) and thiobenzianilide (**5a**; 65%). A similar reaction of **4** with N-*p*-tolylbenzimidoyl



Scheme 1

Table 1—Characterization Data of Dimidoyl Sulphides (3), Anilides (5) and N-Aryl-N′-phenylbenzamidines (6)

Compd	R	m.p. (lit. m.p.) °C	Yield (%)	Mol. formula (M^+)	Analysis %		PMR (δ, ppm)
					Found	Calc.	
3a	H	199-200 (202-4)[10]	82	$C_{26}H_{20}N_2S$ (392)	C 79.6 H 5.1 N 7.1	79.1 5.2 7.0	6.8-7.5 (*m*, 20H, Ar-*H*)
3b	*p*-CH_3	138	80	$C_{28}H_{24}N_2S$ (420)	80.0 5.7 6.7	79.3 5.8 6.2	2.19 (*s*, 6H, 2 × CH_3) 6.8-7.5 (*m*, 18H, Ar-*H*)
3c	*o*-Cl	123-24	79	$C_{26}H_{18}Cl_2N_2S$ (461)	67.7 3.8 6.1	67.4 3.8 5.9	6.8-7.5 (*m*, 18H, Ar-*H*)
3d	*m*-Cl	101	76	$C_{26}H_{18}Cl_2N_2S$	67.7 3.9 6.1	67.0 3.7 5.9	6.8-7.5 (*m*, 18H, Ar-*H*)
3e	*p*-Cl	145	81	$C_{26}H_{18}Cl_2N_2S$	67.7 3.9 6.1	66.9 3.8 6.2	6.8-7.5 (*m*, 18H, Ar-*H*)
3f	*p*-Br	175	78.5	$C_{26}H_{18}Br_2N_2S$	56.7 3.3 5.1	57.0 3.1 5.3	6.8-7.5 (*m*, 18H, Ar-*H*)
5a	H	100	65	$C_{13}H_{11}NS$	73.2 5.2 6.6	73.7 5.2 7.0	9.2 (*br*, 1H, NH) 6.8-7.5 (*m*, 10H, Ar-*H*)
5b	*p*-CH_3	127 (128-29)[12]	68	$C_{14}H_{13}NS$ (227)	74.0 5.7 6.2	74.7 5.7 6.4	2.29 (*s*, 3H, CH_3), 9.13 (*br*, 1H, NH), 6.8-7.5 (*m*, 9H, Ar-*H*)
5c	*p*-Cl	147-48 (149)[13]	75	$C_{13}H_{10}NSCl$ (247)	63.0 4.0 5.7	63.2 4.1 5.7	9.16 (*br*, 1H, NH), 6.8-7.5 (*m*, 9H, Ar-*H*)
5d	*p*-Br	142	72	$C_{13}H_{10}BrNS$ (292)	53.4 3.4 4.8	53.5 3.5 4.8	9.13 (*br*, 1H, NH), 6.8-7.5 (*m*, 9H, Ar-*H*)
6a	H	143-44 (144)[14]	33	$C_{19}H_{16}N_2$	83.8 5.9 10.3	83.8 5.9 10.2	—
6b	*p*-CH_3	131 (133)[15]	30	$C_{20}H_{18}N_2$	83.9 6.3 9.8	84.01 6.3 9.9	—

chloride (**2b**) resulted in a mixture of N-*p*-tolyl-N′-phenylbenzamidine (**6b**; 30%) and N-*p*-tolylthiobenzanilide (**5b**; 68%). The reaction of **4** with all other imidoyl chlorides (**2c.d**) resulted in thiobenzanilides (**5c.d**) as the only isolable products. The formation of **5** and **6** in these reactions could be rationalised by mechanistic pathways shown in Scheme 2. As shown in this scheme the reactions of **4** with **2** perhaps follow two different pathways, reaction pathway-I leading the formation of thiobenzanilides (**5**) whereas reaction pathway-II resulting in the formation of N-aryl-N′-phenylbenzamidines (**6**). The structure of these products were elucidated on the basis of analytical and spectral data (Table 1).

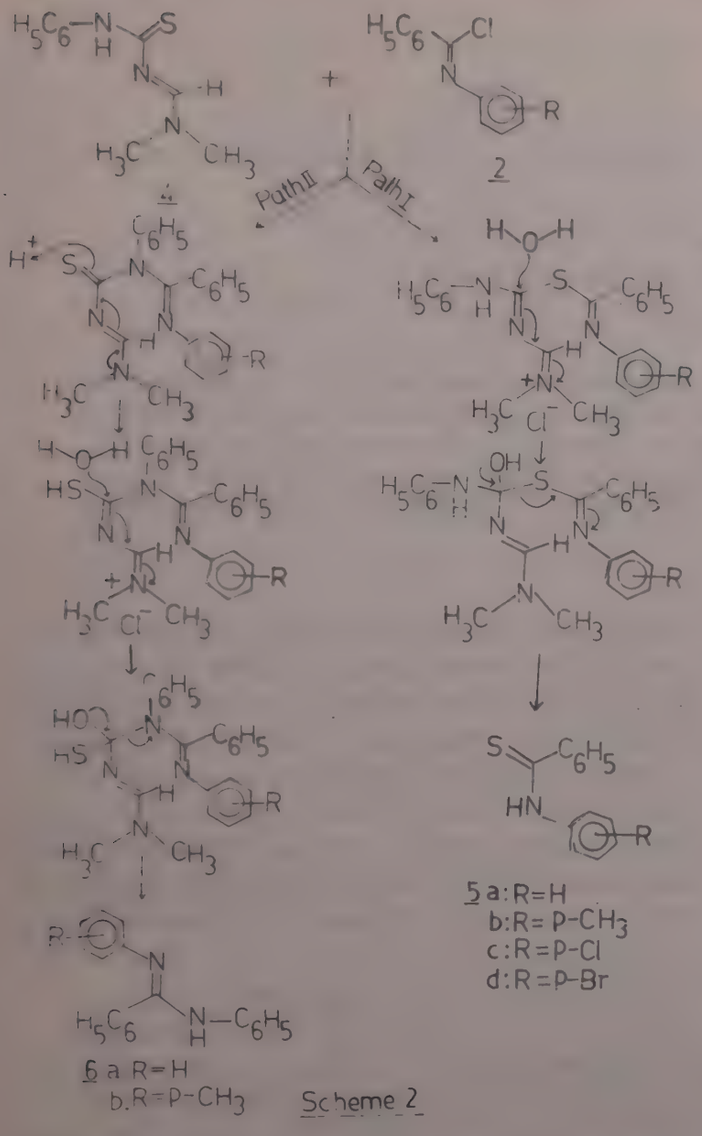
Experimental Procedure

All melting points are uncorrected. The IR spectra were recorded in KBr on a Perkin-Elmer model 297-IR spectrophotometer (ν_{max} in cm^{-1}), and PMR in $CDCl_3$ on a Varian EM-390 90 MHz NMR instrument (chemical shifts in δ, ppm).

N,N-Dimethyl-N′-thiobenzoylformamidine (**1**)[6], N,N-dimethyl-N′-phenylthiocarbamoylformamidine (**4**)[7] and N-arylbenzimidoyl chlorides (**2**)[8] were prepared by literature methods.

Reaction of N,N-dimethyl-N′-thiobenzoylformamidine (**1**) *with N-arylbenzimidoylchlorides* (**2**): *Formation of dimidoylsulphides* (**3**; *Table* 1)

To a stirred solution of **1** (0.7 g, 0.0036 mol) in dry chloroform (30 ml) was added N-phenylbenzimidoyl chloride (**2a**, 0.86 g, 0.0040 mol), and the reaction mixture stirred at room temperature for 1 hr. The residue obtained after careful removal of the solvent under reduced pressure was stirred with aq. ethanol (75%). The solid thus obtained (1.15 g; 82%) was recrystallised from benzene-hexane (1:1) and characte-



Scheme 2

rised as dibenzimidoyl sulphide (**3a**)[9,10], m.p. 199-200° (lit.[10], m.p. 202-44°); IR: 1625, 1495, 1360. (Found: C, 79.1; H, 5.2; N, 7.0. Calc. for $C_{26}H_{20}N_2S$: C, 79.6; H, 5.10; N, 7.14%). MS: *m/z* 392 (M^+).

Reaction of all other N-arylbenzimidoyl chlorides (**2**) with **1** was carried out in a similar manner.

Reaction of N,N-dimethyl-N'-phenylthiocarbamoylformamidine (**4**) *with* **2**

A solution of **4** (0.7 g, 0.0030 mol) and **2a** (0.86 g, 0.0040 mol) in dry THF (25 ml) was refluxed for 5 hr. Removal of the solvent under reduced pressure gave a product mixture which was chromatographed over a silica gel column. Elution with (1:1) mixture of benzene and hexane gave thiobenzanilide (**5a**) (0.39, 65%) which recrystallised from ethanol, m.p. 100° (lit.[11], m.p. 101-2°). IR: 3350-3400, 1510, 1360 (Found: C, 73.7; H, 5.2; N, 7.0. Calc. for $C_{13}H_{11}NS$: C, 73.2; H, 5.2; N, 6.6%); MS: *m/z* 213 (M^+). Continued elution of the column with 1:1 mixture of benzene and hexane gave a compound (0.3 g; 33%) which was recrystallised from benzene and hexane and characterised as N,N'-diphenylbenzamidine (**6a**). m.p. 143-44° (lit.[12], m.p. 144°); IR: 3300, 1595 (Found: C, 83.8; H, 5.9; N, 10.2. Calc. for $C_{19}H_{16}N_2$: C, 83.8; H, 5.9; N, 10.3%); MS: *m/z* 272 (M^+).

The same procedure was followed for the isolation of products from the reactions of all other N-arylbenzimidoyl chlorides (**2**) with **1**. The characterisation data of the various products are given in Table 1.

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Cycloaddition Reactions of Citral Dienamines with 1,4-Quinones†

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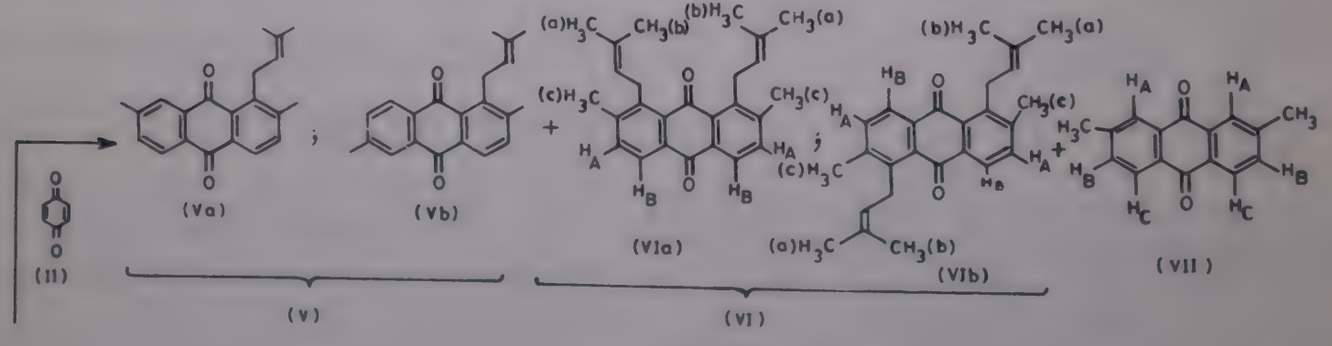
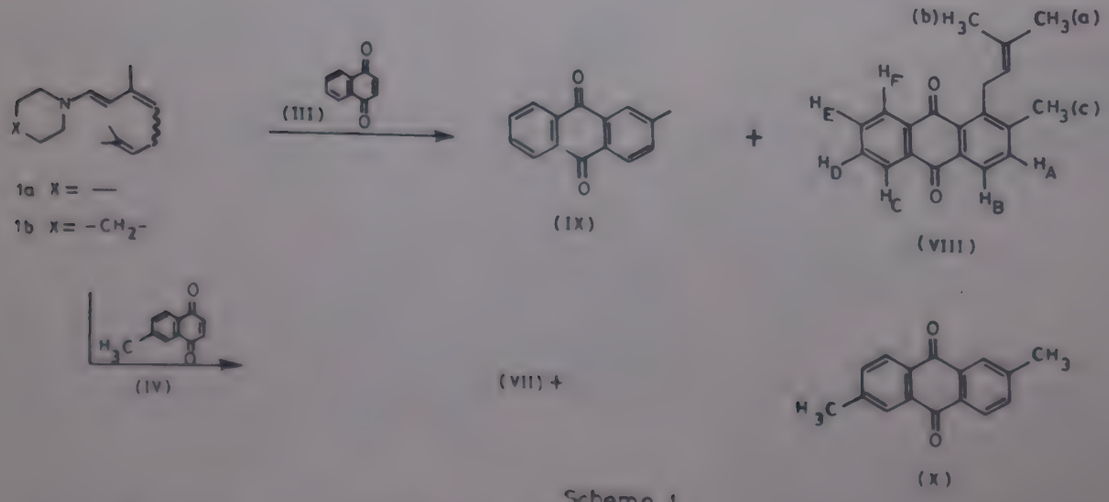
Cycloaddition reactions of citral dienamines (Ia and Ib) with different 1,4-quinones have been investigated and the products formed are characterized. The unusual elimination of isopentenyl side chain during the Diels-Alder reaction of dienamine (Ia or Ib) with quinones, has been found to be consistent. Aromatisation seems to be the driving force for the elimination which involves cleavage of C – C bond under relatively mild condition. Results obtained in the attempted total synthesis of Va, a regioisomer of compound (V), one of the products obtained in the reaction of Ia with *p*-benzoquinone, are also presented.

During our studies on the reactivity of citral dienamines towards different electrophilic olefins[1-3], we observed[1,2] cycloaddition reactions involving unusual elimination of isopentenyl side chain. This observation along with the regioisomeric problem associated with the earlier reported[2] cycloadduct provided impetus to us to reinvestigate the cycloaddition reactions of citral dienamines (Ia and Ib) with *p*-benzoquinone (II), 1,4-naphthoquinone (III) and 6-methyl-1,4-naphthoquinone (IV). The present paper describes the results obtained during the course of these reactions together with the attempted synthesis of one of the regioisomers of compound (V).

Freshly distilled pyrrolidine dienamine (Ia)[4] of citral on condensation with *p*-benzoquinone (II) gave, after column chromatography, VI and VII, albeit in low yields along with the already reported[2] trialkylated anthraquinone (V) (Scheme 1). Compound (VI),





Scheme 1

†Dedicated to Prof. S. Swaminathan on his 60th Birthday celebrations.

$C_{26}H_{28}O_2$ (M^+ 372), m.p. 185-86° was found to be a tetra-alkylated anthraquinone. Its IR (nujol) spectrum exhibited peaks at 1660, 1565 and 735 cm^{-1}. Its UV spectrum in chloroform was typical of anthraquinonoids with maximum absorptions at 263 (ε, 71,280) and 346 nm (6,993). The presence of isopentenyl group [δ 1.71 (6H, *s*, $-CH_3$(a)); 1.82 (6H, *s*, $-CH_3$(b)); 5.10 (2H, *t*, J=6 Hz, $>=<^H$) and 3.92 (4H, *d*, J=6 Hz, benzylic $-CH_2$)], aryl methyl protons [δ 2.44, 6H, *s*, $-CH_3$(c)], and aromatic protons [δ 7.47, 2H, *d*, J=8 Hz, H_A and 7.86, 2H, *d*, J =8 Hz, H_B] was quite evident from the PMR spectrum of VI in $CDCl_3$.

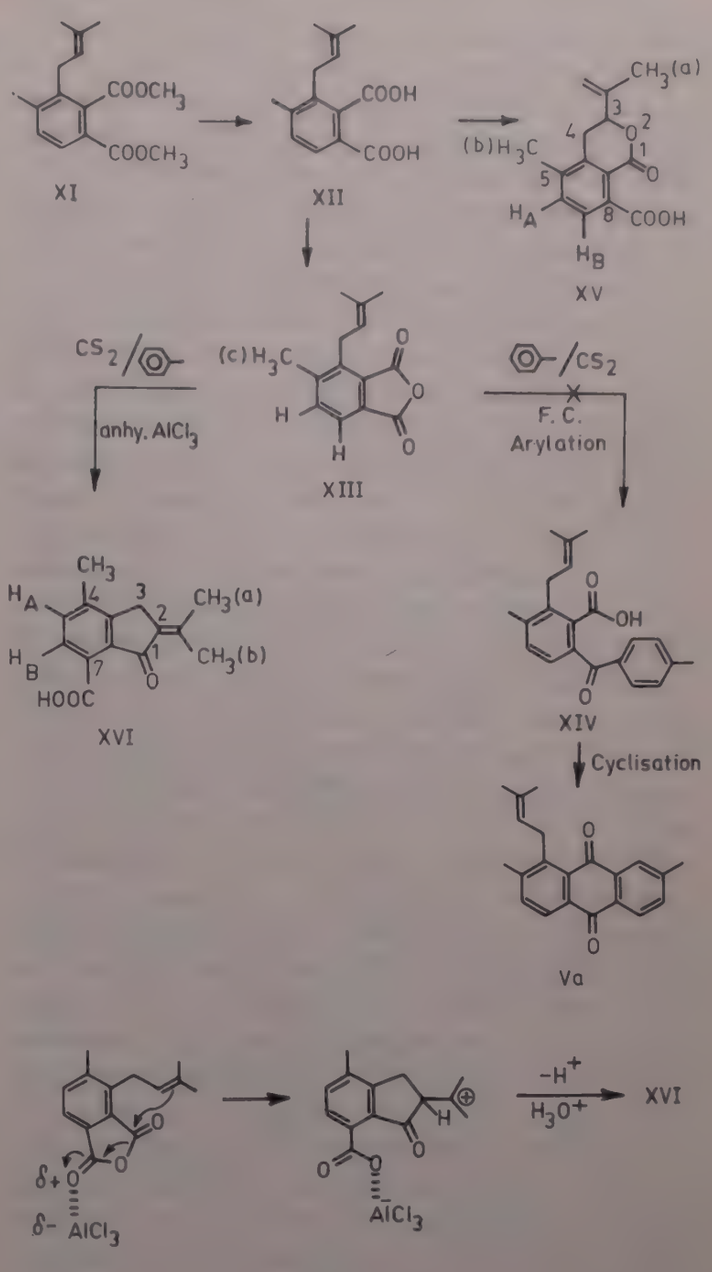
Apparently VI is formed as a result of the structural modifications of the initial cycloadduct. In turn the cycloaddition has occurred by the condensation of 2 mol of Ia with 1 mol of quinone. So compound (VI) could be either 1,8-bis-(3′-methyl-2′-butenyl)-2,7-dimethyl-9,10-anthraquinone (VIa) or 1,5-bis-(3′-methyl-2′-butenyl)-2,6-dimethyl-9,10-anthraquinone (VIb) depending on the mode of addition of diene moiety. Compound (VII) was identified as 2,7-dimethyl-9,10-anthraquinone[5] based on spectral data and direct comparison with an authentic sample[5].

Similarly condensation of piperidine dienamine (Ib)[4] of citral with 1,4-naphthoquinone (III) gave compound (VIII) along with the already reported[1] 2-methyl-9,10-anthraquinone (IX).

Compound (VIII), $C_{20}H_{18}O_2$ (M^+ 290), m.p. 124-25° has been assigned the structure as 1-(3′-methyl-2′-butenyl)-2-methyl-9,10-anthraquinone based on its spectral features (see Experimental). Catalytic hydrogenation of VIII resulted in the formation of 1-(3′-methylbutyl)-2-methyl-9,10-anthraquinone (VIIIa). Similar catalytic hydrogenation of V yielded the corresponding dihydroproduct (VIIIb), the PMR spectrum of which was compatible with the assigned structure. Incidentally in both the cases formation of an unidentified product in minor amounts was observed.

Reaction of 6-methyl-1,4-naphthoquinone[6] with piperidine dienamine (Ib) of citral in dry benzene results in the formation of a mixture of two compounds in around 70%. This mixture contained the two regioisomers VII and X in unequal quantities and the compounds could be separated by fractional crystallisation to give high melting X (m.p. 240-41°) and low melting VII (m.p. 166-67°). These compounds were characterised on the basis of spectral data and direct comparison with respective authentic sample[5].

In order to resolve the regioisomeric problem associated with compounds (V) and (VI) it was felt necessary to synthesize one of the regioisomers of V or VI. Thus it was envisaged that appropriately substituted aromatic anhydride (XIII) (Scheme 2) on



Scheme 1

Friedel-Crafts arylation with toluene should give a ketoacid (XIV) which on cyclodehydration would lead to the regioisomer (Va). Keeping steric demand of the pendent prenyl group in mind, it was assumed that a regioselective arylation of XIII would result in the desired ketoacid (XIV). Based on this strategy dimethyl 3-(3′-methyl-2′-butenyl)-4-methyl-*o*-phthalate (XI)[1] was saponified to furnish the diacid (XII). Compound (XII) was subjected to iodolactonization[7] to give a compound which was characterised as 3-isopropenyl-5-methyl-3,4-dihydroisocoumarin-8-carboxylic acid (XV) based on spectral studies (see Experimental).

The iodolactonization was undertaken with the intention of employing this sequence in deciding the relative dispositions of $-COOH$ and prenyl substituent in the anticipated ketoacid (XIV).

The diacid (XII) was quantitatively converted into the corresponding anhydride (XIII), which was subjected to Friedel-Crafts arylation with toluene in CS_2. Unfortunately the resulting XVI was found to be totally different from the expected ketoacid (XIV). The product XVI has been identified as 2-isopropylidene-4-methylindane-1-one-7-carboxylic acid based on spectral data (see Experimental).

It is evident from the products obtained in the reaction of dienamines of citral with quinones, that the unusual elimination of isopentenyl side chain is observed consistently. Aromatization seems to be the driving force for this elimination which involves cleavage of C−C bond under relatively mild conditions. The formation of V, VI and VIII indicate that aromatization can as well result by the oxidative disproportionation of dihydro intermediate. Compounds VIIIa and VIIIb give an additional proof for the presence of isopentenyl side chain. The formation of compounds (VII), (IX) and (X) in high yields suggest that elimination of isopentenyl side chain leading to aromatization of initial cycloadducts is the favoured path.

In our previous publication[1] we proposed a mechanism for the formation of 2-methylanthraquinone (IX) in the reaction of citral dienamine with 1,4-naphthoquinone (III). On steric grounds we indicated the preferential elimination of secondary amine moiety over that of isopentenyl side chain from the initial cycloadduct. The isolation of compound (VIII) further confirms our earlier proposition.

The key step in the synthesis of the regioisomer (Va) is Friedel-Crafts arylation of the anhydride XIII with toluene. Unfortunately we could not enforce such arylation. This failure could perhaps be due to the poor nucleophilicity of toluene as well as the proximity of the pendent prenyl group. The latter feature is also responsible for the intramolecular alkylation leading to the formation of compound (XVI). This shows that intramolecular alkylation competes with the intermolecular arylation and infact appears to be the decisive factor. A similar type of alkylation has been reported by Krishna Rao and Joseph[8] in the Diels-Alder reaction of ocimene with maleic anhydride.

Though we could not synthesise Va, based on the isolation of VII, structures (Va) and (VIa) are tentatively proposed for compounds (V) and (VI) respectively. A final confirmation of the exact structures can only be arrived at from X-ray crystallographic studies which will be reported elsewhere.

Experimental Procedure

The IR and UV spectra were recorded on Perkin-Elmer 237B and Varian Superscan-3 spectrophotometers respectively. Mass spectra were recorded at 20-30 eV on a Varian MAT 112 mass spectrometer. PMR spectra were recorded on a Varian XL-100 FTNMR instrument at 100 MHz employing TMS as internal reference.

Condensation of citral dienamine (Ia) with p-benzoquinone (II)

Freshly distilled Ia (15.3 g, 0.075 mol) was condensed with *p*-benzoquinone (7.13 g, 0.066 mol) in acetonitrile (180 ml) under the same experimental conditions as reported earlier[2]. The complex reaction mixture was subjected to column chromatography. Ethyl acetate (1.5%)-hexane eluate gave light yellow crystals of compound (VI); 50 mg (0.2%), m.p. 185-86° (Found: C, 83.4; H, 7.4. $C_{26}H_{28}O_2$ requires C, 83.9; H, 7.5%). Initial fractions of ethyl acetate (3%)-hexane eluate gave the known[2] trialkylated anthraquinone (V), 350 mg (2.0%), m.p. 174-75°. The latter fractions gave 2,7-dimethyl-9,10-anthraquinone (VII) which was further purified by recrystallizing from ethanol, 45 mg (0.3%), m.p. 167-68° (lit.[5] 169°) (Found: C, 81.6; H, 5.2. Calc. for $C_{16}H_{12}O_2$: C, 81.4; H, 5.1%).

Condensation of piperidine dienamine (Ib) with 1,4-naphthoquinone (III)

Freshly distilled Ib (11.25 g, 0.05 mol) was condensed with 1,4-naphthoquinone (7.9 g, 0.05 mol) in dry benzene under inert atmosphere at room temperature for 4 hr. The reaction mixture was concentrated *in vacuo* and the residue subjected to column chromatography. Elution with 1% ethyl acetate-hexane eluate gave a yellow solid which recrystallised from hexane to give 0.250 g (1.7%) of 1-(2′-butenyl-3′-methyl)-2-methyl-9,10-anthraquinone (VIII), m.p. 124-25°; IR (nujol): 1670, 1570 and 725 cm^{-1}; UV ($CHCl_3$): 260 (ε 51,060) and 337 nm (7,898): PMR ($CDCl_3$): δ 1.72 [3H, *s*, $-CH_3$(a)], 1.84 [3H, *s*, $-CH_3$(b)], 2.47 [3H, *s*, −CH (c)], 3.97 [2H, *d*, $J=6$ Hz, benzylic $-CH_2-$], 5.10 [1H, *t*, $J=6$ Hz, >=<H], 7.53 [1H, *d*, $J=8$ Hz, H_A], 7.74 [2H, *m*, H_DH_E] and 8.24 [3H, *m*, H_B, H_C and H_F] (Found: C, 82.9; H, 6.4. $C_{20}H_{18}O_2$ requires C, 82.8; H, 6.2%). The known 2-methyl-9,10-anthraquinone[1], m.p. 172-74° was obtained in about 65% yield (7.20 g) on eluting the column with 3% ethyl acetate-hexane.

Hydrogenation of compound V and VIII: General procedure

V or VIII (0.1 g) was dissolved in ethyl acetate (15 ml) and to this was added 5% Pd-C (0.01 g). The reaction mixture was shaken in a Parr hydrogenation unit under 65 psi H_2 pressure for 6 to 8 hr at room temperature. Catalyst was filtered off and the product was purified by column chromatography.

Both compounds VIIIa and VIIIb were found to be thick viscous reddish liquids. VIIIa—IR($CHCl_3$): 1670, 1600, 1580 and 865 cm^{-1}; PMR($CDCl_3$): δ 1.05 [6H, *d*, $J=7$ Hz, $-CH(CH_3)_2$], 1.60-1.90 [3H, complex multiplet, $-CH_2-$ and $-CH<$], 2.40-2.70 [5H, *m*, benzylic-CH_2- and aromatic $-CH_3$] and 7.40-8.40 [6H, complex multiplet, aromatic protons]. VIIIb—IR($CHCl_3$): 1670, 1610, 1580 and 870 cm^{-1}; PMR($CDCl_3$): δ 1.08 [6H, *d*, $J=7$ Hz, $-CH(CH_3)_2$], 1.60-1.80 [3H, complex multiplet, $-CH_2-$ and $-CH<$], 2.40-2.60 [8H, *m*, benzylic-CH_2- and aromatic-CH_3] and 7.40-8.30 [5H, *m*, aromatic protons].

Condensation of Ib with 6-methyl-1,4-naphthoquinone (IV)

Freshly distilled Ib (0.219 g, 0.001 mol) was condensed with IV (0.172 g, 0.001 mol) in dry benzene under inert atmosphere for 4 hr. Removal of solvent *in vacuo* gave a crude solid (0.180 g) which on fractional crystallisation gave 2,6-dimethyl-9,10-anthraquinone (X) (0.08 g), m.p. 240-41° (lit. 242°)[5] and 2,7-dimethyl-9,10-anthraquinone (VII) (0.065 g), m.p. 166-67° (lit. 169°)[5].

Attempted total synthesis of regioisomer (Va) of compound (V): Hydrolysis of compound (XI)

The diester (XI, 0.552 g, 0.002 mol) was dissolved in methanol (10 ml) and to this was added methanolic NaOH (5.716 g in 35 ml). The mixture was refluxed on a water-bath for 3 hr, cooled and concentrated *in vacuo* to give the sodium salt of the diacid (XII) from which the diacid could be recovered by acidifying at low temperature using 5% HCl. It crystallised from water to give soft white crystalline 3-[2′-butenyl-3′-methyl]-4-methyl-O-phthalic acid (XII), yield 60%, m.p. 172-74°; M^+ 248; IR (nujol): 1745, 1675 and 825 cm^{-1}; PMR (acetone-d_6): δ 1.70 [3H, *s*, $-CH_3$(a)], 1.80 [3H, *s*, $-CH_3$(b)], 2.42 [3H, *s*, $-CH_3$(c)], 3.48 [2H, *d*, $J=6$ Hz, benzylic $-CH_2-$], 5.10 [1H, *t*, $J=6$ Hz, $>=<^{H}$], 7.36 [1H, *d*, $J=8$ Hz, H_A] and 7.82 [1H, *d*, $J=8$ Hz, H_B] (Found: C, 68.0; H, 6.9. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5%).

Preparation of anhydride (XIII)

Diacid (XII, 0.25 g) was dissolved in dry benzene (25 ml) and the solution was refluxed for 1.5 hr in the presence of catalytic amount of *p*-toluenesulphonic acid. Reaction product was passed quickly through a short silica gel column to give 3-[2′-butenyl-3′-methyl]-4-methyl phthalic anhydride (XIII) in 93% yield, m.p. 84-86°; M^+ 230; IR(nujol): 1830, 1765 and 885 cm^{-1}; PMR ($CDCl_3$): δ 1.74 [6H, *s*, $=(CH_3)_2$], 2.62 [3H, *s*, $-CH_3$(c)], 3.88 [2H, *d*, $J=7$ Hz, benzylic $-CH_2-$], 5.02 [1H, *t*, $J=7$ Hz, $>=<^{H}$], 7.63 [1H, *d*, $J=6$ Hz, H_A] and 7.74 [1H, *d*, $J=6$ Hz, H_B] (Found C, 73.4; H, 6.2. $C_{14}H_{14}O_3$ requires C, 73.0; H, 6.1%).

Friedel-Crafts reaction of XIII

Anhydrous aluminium chloride (7.86 g, 0.06 mol) was added to a solution of toluene (3.3 ml, 0.03 mol) in dry CS_2 (15 ml). To this suspension was added a solution of XIII (0.7 g, 0.003 mol) in CS_2 (15 ml) during 15 min under N_2 atmosphere. The reaction mixture was vigorously stirred for 10 min, left at room temperature for 2 hr, refluxed on a water-bath for 2.5 hr, cooled and poured over crushed ice (10 g) containing conc. HCl (3 ml). After shaking the mixture, the organic phase was separated, the aqueous phase extracted with $CHCl_3$ and the combined organic extract dried and kept in deep freeze ($-5°$) for 2 days to afford 2-isopropylidene-4-methyl-indane-1-one-7-carboxylic acid (XVI) as yellowish white crystals in about 45% yield, m.p. 206-7°; M^+ 198; IR (nujol): 1725, 1665 and 925 cm^{-1}; PMR ($CDCl_3$): δ 2.20 [3H, *s*, $-CH_3$(a)], 2.50 [3H, *s*, $-CH_3$(b)], 2.55 [3H, *s*, $-CH_3$(c)], 3.62 [2H, *s*, benzylic $-CH_2-$], 7.55 [1H, *d*, $J=8$ Hz, H_A], 8.32 [1H, *d*, $J=8$ Hz, H_B] and 15.31 [1H, *s*, exchangeable with D_2O, $-COOH$] (Found: C, 84.8; H, 6.8. $C_{14}H_{14}O$ requires C, 84.8; H, 7.1%).

Iodolactonization[7] of the diacid (XII)

To a solution obtained by adding the diacid (XII, 0.124 g, 0.5×10^{-3} mol) to 0.5 *M* aqueous $NaHCO_3$ (5 ml) was added a solution of 0.254 g of I_2 (0.1×10^{-3} mol) and 0.5 g of KI (0.3×10^{-3} mol) in water (5 ml). The resulting mixture was allowed to stand in dark for 24 hr with occasional swirling and then extracted with CH_2Cl_2 and $CHCl_3$. Combined organic extract was washed with aq sodium thiosulphate, dried and concentrated to give a white solid which recrystallised from chloroform-hexane to give 3-isopropenyl-5-methyl-3,4-dihydroisocoumarin-8-carboxylic acid (XV) in 30% yield, m.p. 154-56°; M^+ 246; IR (nujol): 1715, 1275, 1010 and 825 cm^{-1}; PMR ($CDCl_3$): δ 1.91 [3H, *s*, $-CH_3$(a)], 2.40 [3H, *s*, $-CH_3$(b)], 3.01 [2H, *d*, $J=8$ Hz, benzylic $-CH_2-$], 4.96 [1H, *t*, $J=8$ Hz, allylic $-CH-$], 5.09 [1H, *bs*, $=$ 1H], 5.99 [1H, *bs*, $=$ H], 7.45 [1H, *d*, $J=8$ Hz, H_A], 7.67 [1H, *d*, $J=8$ Hz, H_B] and 9.10 [1H, *bs*, exchangeable with D_2O, $-COOH$] (Found: C, 67.9; H, 5.5. $C_{14}H_{14}O$ requires C, 68.3; H, 5.7%).

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Phase Transfer Catalysed Hydroxymethylation of 2′-Hydroxydihydrochalcones: A New Synthesis of Homoisoflavanones

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2′-Hydroxydihydrochalcones having different oxygenation patterns in rings A and B, on treatment with formalin in chloroform-saturated aqueous potassium carbonate biphase system in the presence of a phase transfer catalyst (tetra-*n*-butylammonium hydrogen sulphate) give the corresponding α-hydroxymethyl derivatives in excellent yields. These α-hydroxymethyl derivatives on refluxing with 25% aq diethylamine in ethanol undergo facile cyclisation to afford corresponding homoisoflavanones in 80-85% yields.

Hydroxymethylation of *o*-hydroxyphenyl benzyl ketones with formalin under phase transfer catalysed conditions resulting in the formation of the corresponding α-hydroxymethylphenyl benzyl ketones and their conversion into isoflavanones has recently been reported from our laboratory[1]. The present paper deals with hydroxymethylation studies of 2′-hydroxydihydrochalcones.

2′-Hydroxy-4′-methoxydihydrochalcone (**1**) when reacted with formalin in $CHCl_3$-saturated aqueous potassium carbonate biphase system[1] gave a complex mixture. However, in chloroform-30% aqueous potassium carbonate biphase system in the presence of tetra-*n*-butylammonium hydrogen sulphate as a phase transfer catalyst, the above reaction resulted in the formation of compound (A) as a colourless viscous oil, R_f 0.5 (silica gel-G; ethyl acetate-benzene, 1:9).

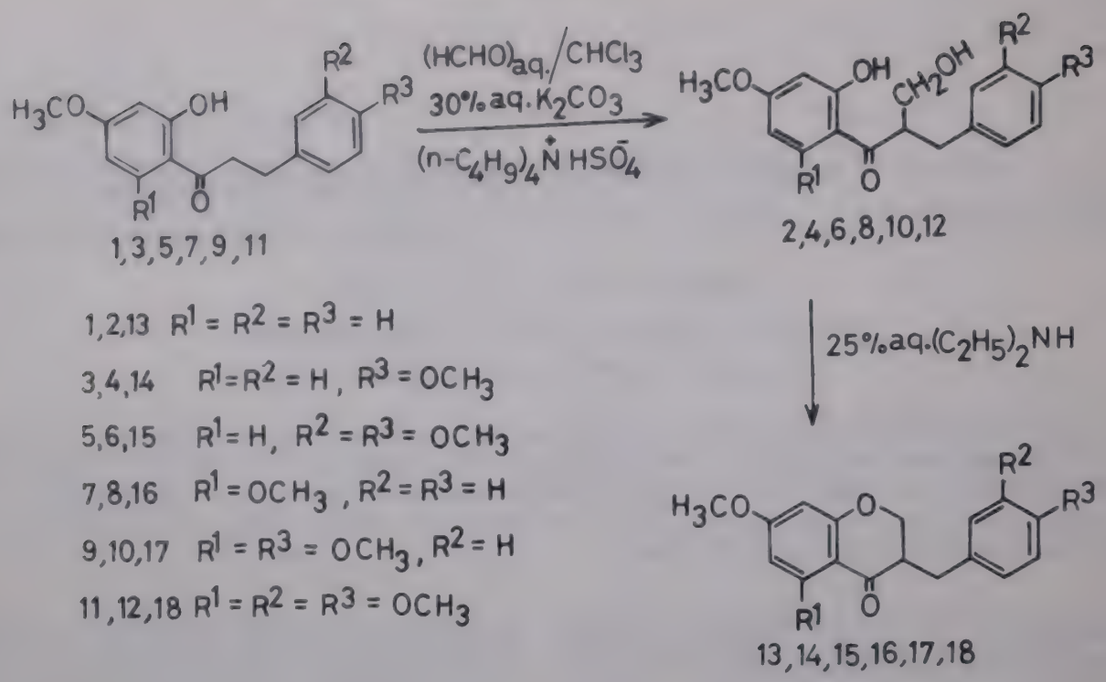
The typical four-proton multiplet at δ 2.90-3.30 in the PMR spectrum of **1**, due to bridge methylene groups, was absent in the PMR spectrum of compound (A), indicating that hydroxymethylation in **1** had taken place at one of the methylene groups. In addition to this the PMR spectrum of compound (A) displayed signals at δ 2.25-2.35 (*bs*, 1H, OH, exchangeable with D_2O), 2.95 (*m*, 2H, CH_2 attached to ring-B), 3.4-4.1 (*bm*, part of it merged with CH_3O signal at δ 3.75, 3H, $-COCHCH_2OH$), 7.6 (*d*, 1H, $J=9$ Hz, H-6′), 6.3 (*m*, 2H, H-3′ and H-5′), 7.20 (*s*, 5H, side phenyl protons) and 13.0 (1H, chelated OH, exchangeable with D_2O). In the mass spectrum compound (A) showed the molecular ion peak at *m/z* 286 (15.6%); other prominent peaks were observed at *m/z* 268 (3.1%, M^+-18), 256 (6%, M^+-30), 255 (28%, M^+-31), 151 (100%) and 91 (12.3%).

Based on these spectral data and colour reactions, compound (A) was assigned the structure as 2′-hydroxy-4′-methoxy-α-hydroxymethyldihydro chalcone (**2**). It, thus, became evident that α-methylene was far more reactive than any of the nuclear positions or the β-methylene, under the conditions of experiment, which is in agreement with reactivity of the methylenes observed in the reaction with ethyl formate[2].

The general applicability of the reaction has been established by subjecting 2′-hydroxy-4,4′-dimethoxy-(**3**), 2′-hydroxy-3,4,4′-trimethoxy-(**5**)-, 2′-hydroxy-4′,6′-dimethoxy-(**7**)-, 2′-hydroxy-4,4′,6′-trimethoxy-(**9**)- and 2′-hydroxy-3,4,4′,6′-tetramethoxy-(**11**)-dihydrochalcones to this reaction. In all cases the corresponding α-hydroxymethyl derivatives, viz. **4** (M^+ 316), **6** (M^+ 346), **8** (M^+ 316), **10** (M^+ 346) and **12** (M^+ 376), structure of which were proved by spectral analyses, were obtained in excellent yields. The presence of the phase transfer catalyst is essential for the efficiency of the reaction, since dihydrochalcones derived from the phloroglucinol unit gave a complex mixture and those possessing a resorcinol unit gave much lower yields when the reaction was carried out in its absence.

We have noticed certain interesting features in the mass spectra of **2**, **4**, **6**, **8**, **10** and **12**. For example these showed a weak molecular ion peak. α-Cleavage of the molecule adjacent to the carbonyl appeared to be the preferred fragmentation as indicated by the base peaks; other prominent peaks appearing at M^+-18, M^+-30 and M^+-31 indicated facile loss of H_2O, CH_2O, H and CH_2O respectively. Fragment ion due to benzylic cleavage was also present in the mass spectra of these compounds.

Having obtained the above 2′-hydroxy-α-hydroxymethyl dihydrochalcones (**2**, **4**, **6**, **8**, **10** and **12**), cyclodehydration of these compounds was carried out, under reflux in the presence of 25% aq. diethylamine in ethanolic medium. Compound (**2**) yielded a viscous oil (compound B) after the removal of solvent (R_f 0.75; silica gel-G; ethyl acetate-benzene, 1:9). It did not give any colour with ethanolic ferric chloride showing the



absence of chelated hydroxyl group. Use of pure diethylamine in ethanol for cyclodehydration[1] in these cases gave a complex reaction product. The structure of compound (B) as 7-methoxyhomoisoflavanone (**13**) was finally confirmed from its PMR spectrum (see Experimental).

This procedure of cyclodehydration was successfully used for the conversion of **4**, **6**, **8**, **10** and **12** into 7,4′-dimethoxy-(**14**)-, 7,3′,4′-trimethoxy-(**15**)-, 5,7-dimethoxy-(**16**)-, 5,7,4′-trimethoxy-(**17**)- and 5,7,3′,4′-tetramethoxy-(**18**)-homoisoflavanones respectively in excellent yields.

Incidentally the present method proves to be superior to the biomimetic synthesis of homoisoflavanones reported from our laboratories[3] involving the reaction of 2′-hydroxydihydrochalcones with diiodomethane. Using this literature method, the desired compound was obtained in ~10% yield and the major product of the reaction was the corresponding bi-dihydrochalconyloxymethane.

Experimental Procedure

2′-Hydroxy-4-methoxy-α-hydroxymethyldihydrochalcone (**2**)

Compound (**1**, 100 mg) was dissolved in chloroform (1.5 ml) and stirred with formalin (1.5 ml) and 30% aq potassium carbonate (1.5 ml) in the presence of tetra-*n*-butylammonium hydrogen sulphate (50 mg). The reaction was monitored by TLC and took nearly 4 hr for completion. Chloroform layer was separated, extracted with aq sodium metabisulphite and washed with water. Chloroform was distilled off and the residue subjected to preparative TLC on silica gel-G using ethyl acetate-benzene (1:9). Band at R_f 0.5, on elution with acetone afforded **2** as colourless viscous oil (95 mg), MS: *m/z* 286 (15.6%, M^+), 268 (3.1, $M^+ - 18$), 256 (6, $M^+ - 30$), 255 (28, $M^+ - 31$), 151 (100), 91 (12.3).

2′-Hydroxy-4,4′-dimethoxy-α-hydroxymethyldihydrochalcone (**4**)

2′-Hydroxy-4,4′-dimethoxydihydrochalcone (**3**, 100 mg) in chloroform on similar treatment with formalin at room temperature for 4 hr gave **4** as a colourless viscous oil (95 mg) R_f 0.49 on silica gel-G in ethyl acetate-benzene, 1:9), PMR($CDCl_3$): δ 2.45 (*bs*, 1H, $-CH_2OH$), 2.90 (*m*, 2H, $-CH_2-Ph$), 3.50-4.10 (*m*, 3H, $-CO-CH$ & $-CH_2OH$), 3.70 and 3.80 (each *s*, 3H each, $2\times-OCH_3$), 6.35 (*m*, 2H, H-3′ & H-5′), 6.70-7.12 (4H, *AA′ BB′* pattern of H-2, H-3, H-5 & H-6), 7.55 (*d*, $J=10$ Hz, 1H, H-6′) and 13.40 (*s*, 1H, chelated $-OH$).

2′-Hydroxy-3,4,4′-trimethoxy-α-hydroxymethyldihydrochalcone (**6**)

Similar reaction of 2′-hydroxy-,3,4,4′-trimethoxydihydrochalcone (**5**, 100 mg) for 4 hr afforded **6** as a colourless viscous oil (95 mg) (R_f 0.45, silica gel-G, ethyl acetate-benzene, 1:9): PMR ($CDCl_3$): δ 2.40 (*bs*, 1H, $-CH_2OH$), 2.85-3.10 (*m*, 2H, $-CH_2Ph$), 3.45-4.12 (*bm*, 3H, $-CO-CH$ & $-CH_2OH$), 3.80-3.90 (*b*, 9H, $3\times-OCH_3$), 6.32-6.38 (*m*, 2H, H-3′ & H-5′), 6.70-6.78 (*m*, 3H, H-2, H-5 & H-6), 7.60 (*d*, $J=9$ Hz, 1H, H-6′) and 13.0 (*s*, 1H, chelated $-OH$).

2′-Hydroxy-4′,6′-dimethoxy-α-hydroxymethyldihydrochalcone (**8**)

It was similarly obtained as a colourless viscous oil starting from 2′-hydroxy-4′,6′-dimethoxydihydro-

chalcone (**7**); R_f 0.43 (silica gel-G, ethyl acetate-benzene, 1:9); PMR($CDCl_3$): δ 2.20 (*bs*, 1H, $-CH_2OH$), 2.85 (*m*, 2H, $-CH_2Ph$), 3.55 (*m*, 1H, $-CO-CH$), 3.70 & 3.80 (each *s*, 3H each, $2\times -OCH_3$), 3.95 (*m*, 2H, $-CH_2OH$), 5.75 (*d*, $J=2$ Hz, 1H, H-3'), 5.90 (*d*, $J=2$ Hz, 1H, H-5), 7.20 (*s*, 5H, $-C_6H_5$) and 13.40 (*s*, 1H, chelated $-OH$).

2'-Hydroxy-4,4',6'-trimethoxy-α-hydroxymethyldihydrochalcone (**10**)

Similar reaction of 2'-hydroxy-4,4',6'-trimethoxydihydrochalcone (**9**) (stirring for 4.5 hr at room temperature) afforded **10** as a colourless viscous oil; R_f 0.4 (silica gel-G, ethyl acetate-benzene, 1:9); PMR($CDCl_3$): δ 2.50 (*s*, 1H, $-CH_2OH$), 2.75-2.97 (*m*, 2H, $-CH_2Ph$), 3.30-4.20 (*bm*, 3H, $-CO-CH$ & CH_2OH), 3.65-3.80 (3*s*, 3H each, 9H, $3\times -OCH_3$), 5.82 (*d*, $J=2$ Hz, 1H, H-5'), 5.97 (*d*, $J=2$ Hz, 1H, H-3'), 6.65-7.07 (4H, *AA' BB'* pattern of H-2, H-3, H-5 & H-6) and 13.90 (*s*, 1H, chelated $-OH$).

2'-Hydroxy-3,4,4',6'-tetramethoxy-α-hydroxymethyldihydrochalcone (**12**)

It was similarly obtained from 2'-hydroxy-3,4,4',6'-tetramethoxydihydrochalcone (**11**) (stirring for 4.5 hr at room temperature) as a buff-coloured solid, which crystallised from benzene-light petroleum as white needles, m.p. 120-21° (Found: C, 63.6; H, 6.6. $C_{20}H_{24}O_7$ requires C, 63.8; H, 6.38%); PMR($CDCl_3$): δ 2.30 (*s*, 1H, $-CH_2OH$), 2.70-2.95 (*m*, 2H, $-CH_2Ph$), 3.45-4.21 (*bm*, 3H, $-CO-CH$ & CH_2OH), 3.70 (*bs*, 12H, $4\times -OCH_3$), 5.80 (*d*, $J=2$ Hz, 1H, H-5'), 5.95 (*d*, $J=2$ Hz, 1H, H-3') and 6.62 (*s*, 3H, H-2, H-5 & H-6).

Cyclisation of **2**, **4**, **6**, **8**, **10** & **12** *with 25% aq diethylamine: Formation of homoisoflavanones* (**13-18**)

A typical procedure starting with **2** is described in the sequel. Compound (**2**, 100 mg) was dissolved in ethanol (10 ml) and refluxed with 25% aq diethylamine (0.1 ml). The reaction was monitored by TLC and took 2 hr for completion. Ethanol was distilled off and the residue dried *in vacuo* over phosphorus pentoxide. The dried residue was subjected to preparative TLC (on silica gel-G, ethyl acetate-benzene, 1:9). The band at R_f 0.75 on elution with acetone afforded homoisoflavanone (**13**) as a colourless viscous oil (75 mg); PMR($CDCl_3$): δ 2.45-2.90 (*m*, 2H, CH_2 at position-9), 3.10-3.40 (*m*, 1H, H-3), 3.80 (*s*, 3H, $-OCH_3$), 4.0-4.30 (*m*, 2H, CH_2 at position-2), 6.25 (*d*, $J=2$ Hz, 1H, H-8), 6.35-6.50 (*dd*, $J=2$ Hz & 10 Hz, 1H, H-6), 7.10 (*s*, 5H, C_6H_5) and 7.75 (*d*, $J=10$ Hz, 1H, H-5).

7,4'-Dimethoxyhomoisoflavanone (**14**, 100 mg) was similarly obtained from **4** as a buff-coloured solid which crystallised from benzene-light petroleum as colourless needles (85 mg), m.p. 72-73° (Found: C, 71.9; H, 6.4. $C_{18}H_{18}O_4$ requires C, 72.2; H, 6.2%); PMR($CDCl_3$): δ 2.55-2.90 (*m*, 2H, CH_2 at position-9), 3.15-3.60 (*m*, 1H, H-3), 3.85, 3.90 (each *s*, 3H each, $2\times -OCH_3$), 4.12-4.55 (*m*, 2H, CH_2 at position-2), 6.50 (*d*, $J=2$ Hz, 1H, H-8), 6.60 (*dd*, $J=2$ Hz & 10 Hz, 1H, H-6), 6.90-7.30 (4H, *AA' BB'* pattern of H-2', H-3', H-5' & H-6') and 7.95 (*d*, $J=10$ Hz, 1H, H-5).

7,3',4'-Trimethoxyhomoisoflavanone (**15**) was likewise obtained as a solid, m.p. 92-93° (lit.[3] m.p. 92-93°) by refluxing **6** with the reagents for 2.5 hr; PMR($CDCl_3$): δ 2.44-3.25 (*m*, 3H, CH_2 at position-9 & H-3), 3.82-3.90 (*bs*, 9H, $3\times -OCH_3$), 4.15-4.32 (*m*, 2H, CH_2 at position-2), 6.35-6.78 (*m*, 5H, H-6, H-8, H-2', H-5' & H-6') and 7.86 (*d*, $J=9$ Hz, 1H, H-5).

5,7-Dimethoxyhomoisoflavanone (**16**) was obtained as a colourless solid by refluxing **8** with the reagents for 2 hr, m.p. 67-68° (lit.[3] m.p. 66-68°); PMR($CDCl_3$): δ 2.54-2.94 (*m*, 2H, CH_2 at position-9), 3.20-3.53 (*m*, 1H, H-3), 3.84 and 3.90 (each *s*, 3H each, $2\times -OCH_3$), 4.03-4.27 (*m*, 2H, CH_2 at position-2), 6.04 (*s*, 2H, H-6 and H-8) and 7.25 (*s*, 5H, $-C_6H_5$).

5,7,4'-Trimethoxyhomoisoflavanone (**17**) was similarly obtained from **10** (refluxing for 2.5 hr). It recrystallised from benzene-light petroleum as colourless needles, m.p. 80-81° (lit.[3] m.p. 80-81°); PMR($CDCl_3$): δ 2.56-2.80 (*m*, 2H, CH_2 at position-9), 3.1-3.52 (*m*, 1H, H-3), 3.80, 3.81 & 3.90 (each *s*, 3H each, $3\times -OCH_3$), 4.0-4.30 (*m*, 2H, CH_2 at position-2), 6.06 (*s*, 2H, H-6 & H-8) and 6.75-7.25 (4H, *AA' BB'* pattern of H-2', H-3', H-5').

5,7,3',4'-Tetramethoxyhomoisoflavanone (**18**) was obtained as a colourless solid by refluxing **12** with the reagents for 2 hr, m.p. 104-105° (Found: C, 66.9; H, 6.5. $C_{20}H_{22}O_6$ requires C, 67.05; H, 6.2%); PMR($CDCl_3$): δ 2.55-2.90 (*m*, 2H, CH_2 at position-9), 3.15-3.45 (*m*, 1H, H-3), 3.85, 4.0 (each *s*, 6H each, $4\times -OCH_3$), 4.05-4.40 (*m*, 2H, CH_2 at position-2), 6.10 (*s*, 2H, H-6 & H-8) and 6.80 (*s*, 3H, H-2', H-5' & H-6').

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Selective Demethylative Cyclisation of 2-Methoxy-allylbenzenes†

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Treatment of 3-substituted 2-methoxyallylbenzenes with dry HBr in $CHCl_3$ causes selective demethylative cyclisation to give 7-substituted 2-methyl-2,3-dihydrobenzofurans. The reaction involves mutual participation of allyl and 2-methoxyl groups and is sterically accelerated by substituents vicinal to OCH_3. The reaction does not take place in high dielectric solvents such as DMF or DMSO. A probable mechanism envisaging a non-classical ionic transition state is proposed and the synthetic utility of this reaction is also demonstrated.

In search for new insecticide synergists, we observed that furapiole (**2**) derived from dillapiole (**1**), a waste product from oil of *Anethum sowa* Roxb., is an excellent potentiator of pyrethrum[1] and carbamate[2] insecticides. The formation of **2** from **1** by HBr in dry $CHCl_3$ in high yield at low temperature involved selective demethylation of the methoxyl group *ortho* to the allyl side chain followed by cyclisation in a concerted fashion[3]. Selective demethylation of substituted anisoles under such mild condition is unique and deserves a more detailed investigation. In this paper, we report such an attempt with a large number of substituted *o*-allylanisoles in order to understand the mechanism and optimum requirements of this reaction.

The 3-methoxyallylbenzenes used were made by the following standard route[4,5]: phenols→allylphenyl ethers→*o*-allylphenols→*o*-allylanisoles. These were characterised by elemental and spectral data. Except the trimethoxyallylbenzenes (**6**, **16** and **26**)[6] and the naturally occurring allyl derivatives, sarisan[7] (**15**) and osmorhizole[8] (**17**), the other *o*-allylanisoles reported now are new. Incidentally synthetic confirmation of the structure, of naturally occurring **15** and **17** is also reported herein for the first time.

The *o*-allylanisoles were treated with dry HBr in $CHCl_3$ at 0°C for 2 hr and the products formed were separated by column chromatography and cnaracterised by spectral data. The yields of products were estimated by HPLC (vide Experimental). Prolonging the reaction period beyond 2 hr did not improve either the yield or the ratio of products formed. Increase in temperature and reaction time for methylenedioxyanisoles caused complications due to formation of polar compounds presumably arising by the cleavage of the methylenedioxy ring.

The results depicted in Scheme I show that in the case of an highly substituted *o*-allylanisole, viz. 2,3-methylenedioxy-4,5,6-trimethoxyallylbenzene (**4**), there is an exclusive formation of 2,3-dihydro-6,7-dimethoxy-2-methyl-4,5-methylenedioxybenzofuran (**5**). The expected HBr addition product, viz. 1-(2′-bromopropyl)-2,3-methylenedioxy-4,5,6-trimethoxybenzene is not formed.

The HPLC analysis of the products from dillapiole (**1**), prepared as reported earlier[1], on the other hand showed that furapiole (**2**) constituted only 80% of the tortal products. The normal HBr addition product (**3**) was formed to the extent of 20% in this case.

Further reduction in the number of ring substituents such as in 2,3,4-trimethoxyallylbenzene (**6**) resulted in the corresponding coumaran (**7**) and the normal addition product (**8**) in 3:2 ratio.

The yield of the dihydrobenzofuran (**10**) from 3-chloro-2-methoxyallylbenzene (**9**) was only 40%. On the other hand, its dimethoxy analogue (**12**) gave the coumaran (**13**) in 30% yield only.

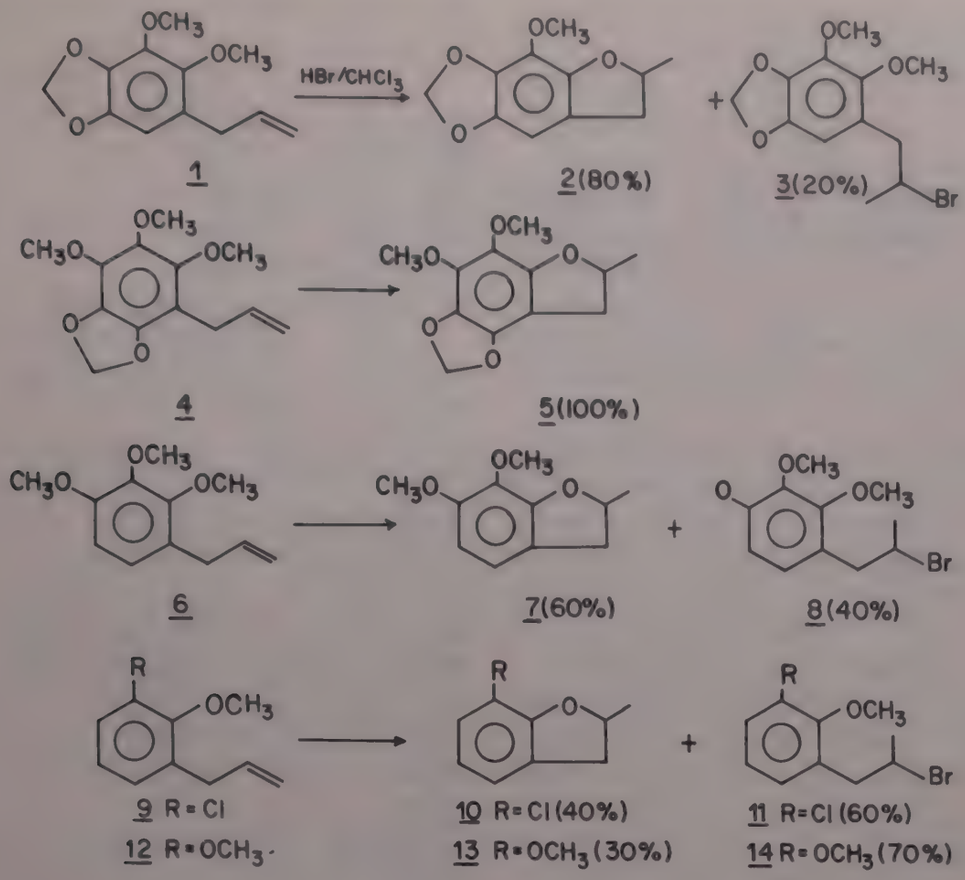
The *o*-allylanisoles (**15-19**) gave exclusively the corresponding normal HBr addition products (**20-24**) with no trace of cyclised products, showing that a substituent in 3-position, i.e. *ortho* to the methoxyl (and *meta* to the allyl group) was essential for this demethylation.

Dihydrodillapiole and its bromo derivative (**3**) on similar treatment with dry HBr, remained unaffected and did not give any demethylated product or furapiole (**2**) showing that the allyl unsaturation was also essential for this demethylation.

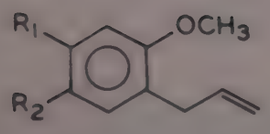
All the title compounds gave, however, exclusively the normal HBr addition products without the formation of the corresponding dihydrobenzofurans when the reaction medium was changed to high dielectric solvent like DMSO or DMF.

It is clear from the above results that this unusual reaction in $CHCl_3$ occurs in the case of only 3-substituted 2-methoxyallylbenzenes and the selectivity of this reaction depends entirely on the steric crowding of the environment vicinal to the 2-methoxyl

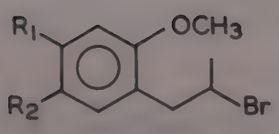
†Contribution No. 304 from the Division of Agricultural Chemicals



Scheme 1



	R_1	R_2
15)	$-OCH_2O-$	
16)	OCH_3	OCH_3
17)	OCH_3	H
18)	H	OCH_3
19)	H	Cl

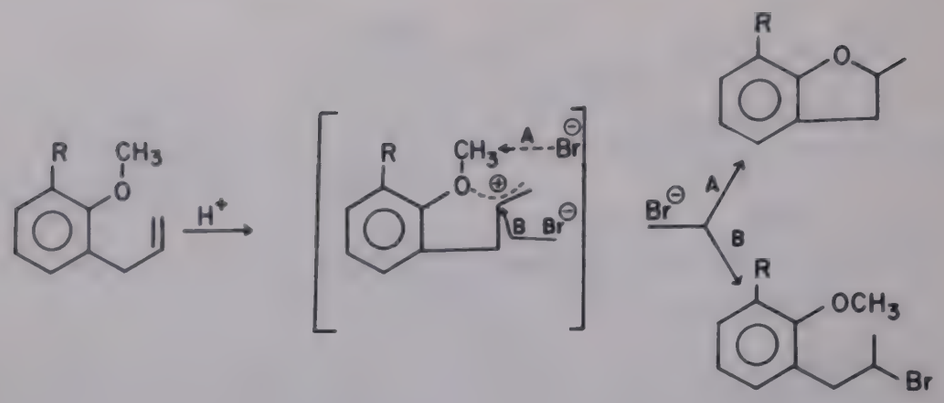


	R_1	R_2
20)	$-OCH_2O-$	
21)	OCH_3	OCH_3
22)	OCH_3	H
23)	H	OCH_3
24)	H	Cl

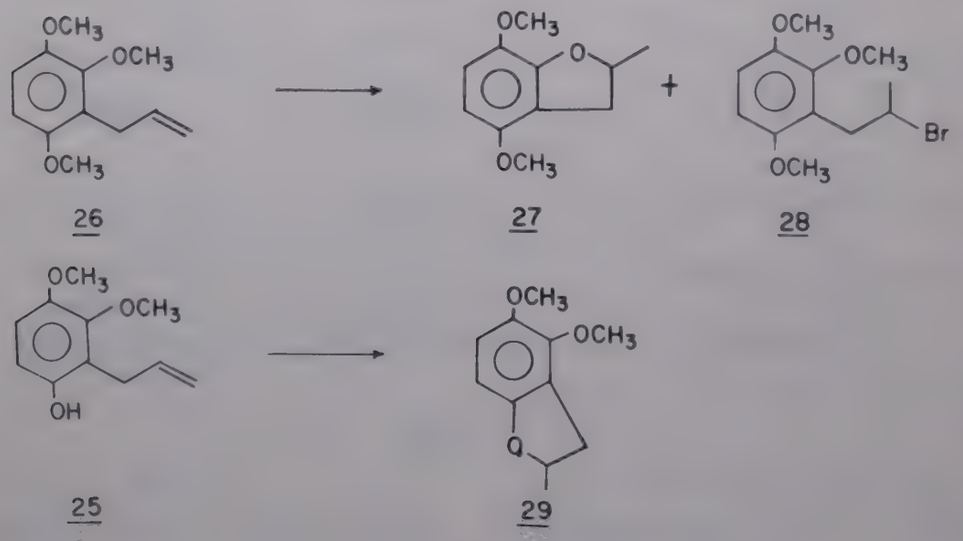
function. The electronic nature of the substitutents seems to have little or no influence on this reaction pathway as is evident from the fact that both deactivating (Cl) and activating (OCH_3) substituents *ortho* (and not *para*) to 2-methoxyl lead to demethylation and formation of dihydrobenzofurans. The apparently better yield of the chlorocoumaran (**10**) in comparison to that of its methoxy analogue (**13**) is, therefore, due to the larger size of the chlorine atom producing greater steric acceleration in the parent anisoles (**9** and **12**) respectively. The stability of dihydrodillapiole under these reaction conditions implies the role of neighbouring allyl group participation in demethylation.

The selectivity of the methoxyl function in undergoing demethylation and the neighbouring allyl group participation phenomenon observed in the above reactions seem to suggest the probable mechanism as shown in Scheme 2, via a non-classical ionic transition state involving both the lone pair of electrons of the methoxyl function and electrons of the allyl double bond after protonation. The formation of such transition state would be facilitated conformation-wise in 2-methoxyallylbenzenes bearing a substituent at position-3 while its stability would be retarded in polar aprotic solvents such as DMF or DMSO as corroborated by experimental evidence. The nature of products would then depend upon the direction of nucleophilic (Br^-) attack on the transition state as indicated in Scheme 2. The failure to detect *o*-allylphenols as intermediates and the stability of the co-products, viz. the brompopropylbenzenes on prolonging the reaction time further suggest that the demethylation and cyclisation processes might be concerted rather than sequential.

The potential synthetic utility of this reaction is illustrated in Scheme 3. The allylbenzene (**26**) containing two methoxyls *ortho* to allylic function undergoes preferential demethylation of the sterically hindered 2-methoxyl alone to give 2,3-dihydro-4,7-dimethoxy-2-methylbenzofuran (**27**). Starting from the



Scheme 2



Scheme 3

same *o*-allylphenol (**25**), one could thus synthesise **27** as well as its analogue **29**, the latter by the direct treatment of **25** with HBr-AcOH.

Experimental Procedure

IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer-457 grating spectrophotometer and PMR spectra on a Varian EM-360, 60 MHz spectrometer using TMS as an internal reference; chemical shifts in δ-scale values. Boiling points are uncorrected. HPLC analysis was carried out using a Spectra-Physics SP-8000-B instrument with SI-100 (250 mm × 4.6 mm) column, *n*-hexane as the mobile phase at a flow rate of 2 ml/min and UV detector at 254 nm.

The trimethoxyallylbenzenes (**6**, **16** and **26**) were synthesised following the reported procedure[6] and were fully characterised by their PMR data.

2,3,4-Trimethoxyallylbenzene (**6**): Colourless oil, b.p. 128-30°/3 mm (reported[9] 127-32°/3 mm) (Found: C, 69.1; H, 7.6. Calc. for $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%); PMR(CCl_4): 3.25 (*d*, J = 8 Hz, 2H, benzylic), 3.75 (*s*, 6H, 2 × OCH_3), 3.82 (*s*, 3H, OCH_3), 5.03 (*bd*, 2H, $=CH_2$), 5.91 (*m*, 1H, $-CH=$), 6.61 (*dd*, J = 9 Hz, 2H, arom-H).

2,4,5-Trimethoxyallylbenzene (**16**): Colourless oil, b.p. 125-26°/10 mm (reported[9] 120°/5 mm) (Found: C, 69.0; H, 7.7%); PMR(CCl_4): 3.22 (*d*, J = 8 Hz, 2H, benzylic), 3.75 (*s*, 9H, 3 × OCH_3), 4.94 (*bd*, 2H, $=CH_2$). 5.82 (*m*, 1H, CH=). 6.45, 6.65 (each *s*, 2H, arom-H).

2,3,6-Trimethoxyallylbenzene (**26**): Colourless oil, b.p. 118-119°/10 mm (Found: C, 69.1; H, 7.7%); PMR(CCl_4): 3.18 (*d*, J = 8 Hz, 2H, benzylic), 3.75, 3.83 (*s*, 6H, 3H, 3 × OCH_3), 4.96 (*bd*, 2H, $=CH_2$) 5.82 (*m*, 1H, $-CH=$), 6.65 (*dd*, J = 9 Hz, 2H, arom-H).

General procedure for preparation of other o-allylanisoles

The *o*-allylanisoles listed in the sequel were obtained by methylation of the corresponding *o*-allylphenols by CH_3I-K_2CO_3-acetone method. Phenols in turn were prepared as reported earlier[4,5,10,11].

2,3-Methylenedioxy-4,5,6-trimethoxyallylbenzene (**4**): Colourless oil; b.p. 135-7°/10 mm (Found: C, 61.8; H, 6.3. $C_{13}H_{16}O_5$ requires C, 61.9; H, 6.4%); PMR($CDCl_3$): 3.10 (*d*, J = 8 Hz, 2H, benzylic), 3.72 (*s*, 3H, OCH_3), 3.91 (*s*, 6H, 2 × OCH_3), 4.91 (*bd*, 2H, $=CH_2$), 5.73 (*m*, 1H, $-CH=$), 5.80 (*s*, 2H, OCH_2O).

3-Chloro-2-methoxyallylbenzene (**9**): Colourless oil; b.p. 102-3°/10 mm (Found: C, 65.4; H, 5.9; Cl, 19.3. $C_{10}H_{11}ClO$ requires C, 65.8; H, 6.1; Cl, 19.4%); PMR(CCl_4): 3.25 (*d*, J=3 Hz, 2H, benzylic), 3.75, 3.83 (each *s*, 3H each, 2×OCH_3), 5.05 (*bd*, 2H, $=CH_2$), 5.91 (*m*, 1H, $-CH=$), 6.73 (*m*, 3H, arom-H).

Sarisan (**15**): Colourless oil; b.p. 86-87°/0.5 mm (Found: C, 68.6; H, 6.2. $C_{11}H_{13}O_2$ requires C, 68.8; H, 6.3%). Its PMR and IR spectral data were similar to those reported for the natural sarisan[7].

Osmorhizole (**17**): Colourless oil; b.p. 71-2°/2 mm (reported[8] for natural **17**: 71.2°/2 mm) (Found: C, 74.0; H, 7.9. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%); PMR(CCl_4): 3.22 (*d*, J=8 Hz, 2H, benzylic), 3.70, 3.75 (each *s*, 6H, 2×OCH_3), 5.05 (*bd*, 2H, $=CH_2$), 5.92 (*m*, 1H, $-CH=$), 6.43 (*d*, J=3 Hz, 1H, arom-H), 6.75 (*m*, 2H, arom-H).

2,5-Dimethoxyallylbenzene (**18**): Colourless oil; b.p. 120-21°/10 mm (Found: C, 73.9; H, 7.8. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%); PMR(CCl_4): 3.20 (*d*, J=8 Hz, 2H, benzylic), 3.70, 3.75 (each *s*, 6H, 2×OCH_3), 4.95 (*bd*, 2H, $=CH_2$), 5.85 (*m*, 1H, $-CH=$), 6.82 (*m*, 3H, arom-H).

5-Chloro-2-methoxyallylbenzene (**19**): Colourless oil; b.p. 115-16°/10 mm (Found: C, 65.2; H, 5.9; Cl, 19.3. $C_{10}H_{11}ClO$ requires C, 65.8; H, 6.1; Cl, 19.4%); PMR(CCl_4): 3.20 (*d*, J=8 Hz, 2H, benzylic), 3.75 (*s*, 3H, OCH_3), 5.0 (*bd*, 2H, $=CH_2$), 5.82 (*m*, 1H, $-CH=$), 6.64 (*d*, J=9 Hz, 1H, arom-H), 7.0 (*m*, 2H, arom-H).

General procedure for the reaction of HBr with o-allylanisoles

A current of dry HBr gas was bubbled through ice-cold solutions of *o*-allylanisoles (5 mmol) in dry $CHCl_3$ (20 ml) till saturation. After 2 hr of standing at 0°C, the reaction mixtures were decomposed by pouring into ice-water (100 ml), the $CHCl_3$ layer repeatedly washed with water till neutral, dried (Na_2SO_4) and concentrated to furnish light brownish oily residues (yield ≥95%). A small sample in each case was preserved for HPLC using authentic samples of the compounds obtained after purification of the reaction products. A portion of the product residue in ether was extracted with ice-cold 10% methanolic KOH to separate any phenolic product. In all the cases, no such product was formed in detectable amounts.

The TLC of the products revealed that the reaction products from **6**, **9**, **12** and **26** were binary mixtures while others were single. The individual components of the binary mixtures were separated by column chromatography as described below.

The product mixture from **6** (300 mg) loaded over silica gel (25 g) was eluted first with hexane (100 ml) followed by hexane-benzene (4:1, 5×60 ml and 1:1, 3×50 ml). Elution with hexane-benzene (4:1) furnished light brown oil (150 mg) which was characterised as **8** while elution with hexane-benzene (1:1) gave **7** as a colourless oil (90 mg).

Analytical grade products such as **5** and **20-24** were obtained by passing the crude products through a short column of silica gel, eluting the column with hexane-benzene (9:1).

2,3-Dihydro-6,7-dimethoxy-2-methyl-4,5-methylenedioxybenzofuran (**5**) was obtained from **4** and it was found to be identical with a synthetic sample prepared earlier[11].

2,3-Dihydro-6,7-dimethoxy-2-methylbenzofuran (**7**): Colourless oil (Found: C, 67.9; H, 7.2. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.3%); PMR(CCl_4): 1.42 (*d*, J=8 Hz, 2H, $-CHCH_3$), 3.05 (*dq*, 2H, benzylic), 3.75, 3.87 (each *s*, 6H, 2×OCH_3), 5.07 (*m*, 1H, $-CHCH_3$), 6.61 (*dd*, J=9 Hz, 2H, arom-H).

1-(2-Bromopropyl)-2,3,4-trimethoxybenzene (**8**): Light brownish oil (Found: C, 49.5; H, 5.7; Br, 27.5. $C_{12}H_{17}BrO_3$ requires C, 49.8; H, 5.8; Br, 27.6%); PMR (CCl_4): 1.52 (*d*, J=8 Hz, 3H, $-CHBr-CH_3$), 3.00 (*d*, J=8 Hz, 2H, benzylic), 3.72 (*s*, 6H, 2×OCH_3), 3.84 (*s*, 3H, OCH_3), 4.81 (*m*, 1H, $-CHBr-$), 6.44, 6.73 (each *d*, J=9 Hz, 2H, arom-H).

7-Chloro-2,3-dihydro-2-methylbenzofuran (**10**): Colourless oil. Spectral data identical with those reported earlier[12].

1-(2-Bromopropyl)-3-chloro-2-methoxybenzene (**11**): Light brownish oil (Found: C, 45.2; H, 4.5; Br, 30.4; Cl, 13.3. $C_{10}H_{12}BrClO$ requires C, 45.6; H, 4.6; Br, 30.3; Cl, 13.5%); PMR(CCl_4): 1.65 (*d*, J=7.5 Hz, 3H, $-CHBr-CH_3$), 3.10 (*d*, J=8 Hz, 2H, benzylic), 3.85 (*s*, 3H, OCH_3), 4.32 (*m*, 1H, $-CHBr-$), 7.03 (*m*, 3H, arom-H).

2,3-Dihydro-7-methoxy-2-methylbenzofuran (**13**): Colourless oil (Found: C, 73.2; H, 7.3. $C_{10}H_{12}O_2$ requires C, 73.2; H, 7.4%); PMR(CCl_4): 1.45 (*d*, J=7.5 Hz, 3H, $-CHCH_3$), 3.16 (*dq*, 2H, benzylic), 3.82 (*s*, 3H, OCH_3), 5.05 (*m*, 1H, $OCH-$Me), 6.80 (*m*, 3H, arom-H).

1-(2′-Bromopropyl)-2,3-dimethoxybenzene (**14**): Light yellow oil (Found: C, 51.1; H, 5.7; Br, 30.8. $C_{11}H_{15}BrO_2$ requires C, 51.0; H, 5.8; Br, 30.8%); PMR(CCl_4): 1.45 (*d*, J=7.5 Hz, 2H, $-CHCH_3$), 3.20 (*d*, J=8 Hz, 2H, benzylic), 3.70, 3.76 (*s* each, 6H, 2×OCH_3), 4.22 (*m*, 1H, $-CHBr-$), 6.85 (*m*, 3H, arom-H).

1-(2′-Bromopropyl)-2-methoxy-4,5-methylenedioxybenzene (**20**): Colourless oil turning yellow on standing (Found: C, 48.1; H, 4.7; Br, 29.0. $C_{11}H_{13}BrO_3$ requires C, 48.4; H, 4.8; Br, 29.3%); PMR(CCl_4): 1.35 (*d*, J=8 Hz, 3H, $-CHBrCH_3$), 2.75 (*dd*, J=8 Hz, 1H, $CHBr-$), 5.82 (*s*, 2H, OCH_2O), 6.23, 6.45 (each *s*, 2H, arom-H).

1-(2′-Bromopropyl)2,4,5-trimethoxybenzene (**21**): Light yellow oil (Found: C, 49.7; H, 5.7; Br, 27.4. $C_{12}H_{17}BrO_3$ requires C, 49.8; H, 5.9; Br, 27.6%); PMR(CCl_4): 1.45 (*d*, J=7.5 Hz, 2H, $-CHBrCH$), 2.95 (*d*, J=8 Hz, 2H, benzylic), 3.75 (*s*, 6H, 2×OCH_3), 3.82 (*s*, 3H, OCH_3), 6.45, 6.65 (each *s*, 2H, arom-H).

1-(2′-Bromopropyl)-2,4-dimethoxybenzene (**22**): Colourless oil, (Found: C, 51.1; H, 5.8; Br, 30.9. $C_{11}H_{15}BrO_2$ requires C, 51.0; H, 5.8; Br, 30.8%); PMR(CCl_4): 1.33 (*d*, J=7.5 Hz, 3H, $-CHBr-CH_3$), 3.07 (*d*, J=8 Hz, 2H, benzylic), 3.75 (*s*, 6H, 2×OCH_3), 4.44 (*m*, 1H, $-CHBr-$), 6.83 (*m*, 3H, arom-H).

1-(2′-Bromopropyl)-2,5-dimethoxybenzene (**23**): Colourless oil, (Found: C, 50.7; H, 5.7; Br, 30.5%); PMR(CCl_4): 1.55 (*d*, J=7.5 Hz, 3H, $-CHBrCH_3$), 2.96 (*d*, J=8 Hz, 2H, benzylic), 3.72, 3.78 (each *s*, 6H, 2×OCH_3), 4.35 (*m*, 1H, $-CHBr-$), 6.85 (*m*, 3H, arom-H).

1-(2-Bromopropyl)-5-chloro-2-methoxybenzene (**24**): Light yellow oil (Found: C, 45.2; H, 4.5; Br, 30.1; Cl, 13.4. $C_{10}H_{12}BrClO$ requires C, 45.6; H, 4.6; Br, 30.3; Cl, 13.5%); PMR(CCl_4): 1.62 (*d*, J=7.5 Hz, 3H, $-CHBrCH_3$), 3.08 (*d*, J=8 Hz, 2H, benzylic), 3.72 (*s*, 3H, OCH_3), 4.33 (*m*, 1H, $-CHBr-$), 6.91 (*m*, 3H, arom-H).

2,3-Dihydro-4,7-dimethoxy-2-methylbenzofuran (**27**): Colourless oil (Found: C, 68.1; H, 7.2. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.3%); PMR(CCl_4): 1.65 (*d*, J=7.5 Hz, 3H, $-CHCH_3$), 3.14 (*dq*, 2H, benzylic), 3.72, 3.75 (each *s*, 6H, 2×OCH_3), 5.12 (*m*, 1H, $-OCH-$), 6.45 (*dd*, J=9 Hz, 2H, arom-H).

1-(2-Bromopropyl)-2,3,6-trimethoxybenzene (**28**): Colourless oil (Found: C, 49.5; H, 5.7; Br, 27.6. $C_{12}H_{17}BrO_3$ requires C, 49.8; H, 5.7; Br, 27.6%); PMR(CCl_4): 1.35 (*d*, J=7.5 Hz, 3H, $-CHBrCH_3$), 3.15 (*d*, J=8 Hz, 2H, benzylic), 3.78 (*s*, 6H, 2×OCH_3), 3.85 (*s*, 3H, OCH_3), 6.44 (*dd*, J=10 Hz, 2H, arom-H).

Reaction of o-allylanisoles with HBr in DMF or DMSO

An ice-cold solution of an *o*-allylanisole (100 mg) in dry DMF or DMSO (10 ml) was saturated with dry HBr and after 2 hr of standing was worked-up as described above. The products were found to consist only of the bromopropylbenzenes, whose characterisation data are given above.

1-(2′-Bromopropyl)-2,3-methylenedioxy-4,5,6-trimethoxybenzene

The HBr reaction of **4** in DMF or DMSO as above gave this product which was purified by passing through a short column of silica gel with hexane-benzene (4:1) elution. Light brownish oil (Found: C, 61.5; H, 6.7; Br, 31.4. $C_{13}H_{17}BrO_5$ requires C, 61.7; H, 6.8; Br, 31.7%); PMR($CDCl_3$): 1.35 (*d*, J=8 Hz, eH, $-CHBrCH_3$), 3.16 (*d*, J=7.5 Hz, 2H, benzylic), 3.72 (*s*, 3H, OCH_3), 3.91 (*s*, 6H, 2×OCH_3), 5.80 (*s*, 2H, OCH_2O).

2,3-Dihydro-4,5-dimethoxy-2-methylbenzofuran (**29**)

2-Allyl-3,4-dimethoxyphenol[6] (**25**, 200 mg) in gl acetic acid (1 ml) was treated with 48% aq HBr (0.5 ml) and heated at 60-70°C for 3 hr over a water-bath. The reaction mixture was poured into cold water (20 ml), extracted with ether (25 ml), ethereal layer washed with 10 ml each of water, satd $NaHCO_3$ solution and 10% methanolic NaOH and finally with water till neutral. The residue after evaporation of the solvent was passed through a short column of silica gel. Eluting the column with hexane-benzene (4:1) furnished **29** as a colourless oil; yield 140 mg. (Found: C, 67.9; H, 7.2. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.3%); PMR(CCl_4): 1.45 (*d*, J=7.5 Hz, 3H, $-CHCH_3$), 3.13 (*dq*, 2H, benzylic), 3.72, 3.88 (each *s*, 6H, 2×OCH_3), 6.35, 6.45 (each *d*, J=10 Hz, 2H, arom-H).

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Synthesis of New 4-Substituted Xanthotoxins

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A series of 4-substituted xanthotoxins (**3-9** and **10-17**) have been synthesized by the reaction of 4-chloromethylxanthotoxin (**1**) and 4-formylxanthotoxin (**2**) respectively with different reagents.

Xanthotoxin is a well known drug for the treatment of leucoderma[1], sunburn[2] and vitilgo[3]. The naturally occurring xanthotoxin derivative, isopimpinilin is reported to possess molluscicidal activity[4]. A large number of xanthotoxin derivatives have also been synthesized[5-8] of which some are found to exhibit antimicrobial activity[7]. In continuation of our endeavour to buildup biologically active compounds from xanthotoxin, herein we report the synthesis of a series of 4-substituted xanthotoxins (**3-17**) from 4-chloromethylxanthotoxin (**1**) and 4-formylxanthotoxin (**2**) prepared earlier in our laboratory[8].

Reduction (Zn dust/OHAc) of **1** afforded 4-methylxanthotoxin (**3**). Potassium thiocyanate and thiourea reacted with **1** to give 4-thiocyanomethylxanthotoxin (**4**) and 4-(amidinothiomethyl)-xanthotoxin hydrochloride (**5**) respectively. Thiosemicarbazide behaved similarly as thiourea and afforded 4-(thiosemicarbazidomethyl) xanthotoxin hydrochloride (**6**). The structural assignment of compounds **3-6** is based on their IR and PMR data.

Compound **5** when heated with aq. sodium hydroxide furnished, instead of the expected 4-mercaptomethylxanthotoxin, 9-hydroxy-10-methoxy-5-thia-6-oxohept-8-eno [4,5-*c*] benzofuran (**7**) (Scheme 1). The IR spectrum of **7** exhibited strong peaks at 3450 (OH, phenolic) and at 1700 cm^{-1} ($\nu C=O$ group, which differs from the C=O group of lactone ring of the mother compound). The PMR spectrum of **7** displayed signals at δ 3.31 (*s*, 3H, OCH_3), 4.0 (*s*, 2H, methylene), 4.35 and 4.90 (doublet each, 1H each, C-7 and C-8 proton of the thiaoxepin ring) and 6.85 and 7.85 (doublet each, 1H each, $J = 3$ Hz, C-3 and C-2 furanoid protons). The OH proton appeared at δ 9.25. Similar ring-opening and rearrangement was found during methylation of 4-hydroxymethylcanthotoxin[8]. Reaction of **1** with dimethylformamide gave 4-(N, N-dimethylacetamido) xanthotoxin (**8**) which was reduced with equimolar amount of $LiAl(OC_2H_5)_2H_2$ (prepared from $LiAlH_4$ and C_2H_5OH)[9] to afford xanthotoxin-4-acetaldehyde (**9**) (Scheme 1). The PMR spectrum of **9** exhibited signals at δ 4.18 (*s*, 3H, OCH_3), 5.17 (*s*, 2H, methylene), 6.60, 8.57 (doublets each, 1H each, $J = 10$ Hz, C-6 and C-5 protons) and 7.50, 8.23 (doublets each, 1H each, $J = 3$ Hz, C-3, C-2 furanoid protons). The aldehydic proton appeared at δ 9.50.

Reaction of 4-formylxanthotoxin (**2**) with aliphatic and aromatic amines was very sluggish of no synthetic utility. However **2** reacted readily with phenylhydrazine and hydroxylamine to give hydrazo derivative (**10**) and the aldoxime derivative (**11**) respectively. Acetylation of **11** with acetic anhydride and acetic acid afforded the oxime acetate (**12**) while its acetylation with refluxing acetic anhydride gave the corresponding 4-cyanoxanthotoxin (**13**) which could also be prepared by melting the aldoxime acetate (**12**). Condensation of **2** with hydrazine hydrate yielded the dimeric compound (**14**). Furthermore, **2** reacted with ethyl acetoacetate in the presence of triethylamine as catalyst to give the corresponding 4-[(1-cyano-1-ethoxycarbonyl) ethylen-2-yl] xanthotoxin (**15**). Rhodanine also reacted smoothly with **2** either in the presence of acetic acid and anhydrous sodium acetate or in ethanol using triethylamine as a catalyst to give the arylidene derivative (**16**) in quantitative yield. Treatment of **16** with piperidine in refluxing *n*-butanol afforded the piperidino derivative (**17**) with the evolution of H_2S (Scheme 2).

Experimental Procedure

Melting points were determined on a melting point microscope and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 grating spectrophotometer and PMR spectra on a Varian A-60 instrument using TMS as internal reference. The purity of the compounds was checked by TLC on silica gel G plates and the spots were located on irradiation with UV.

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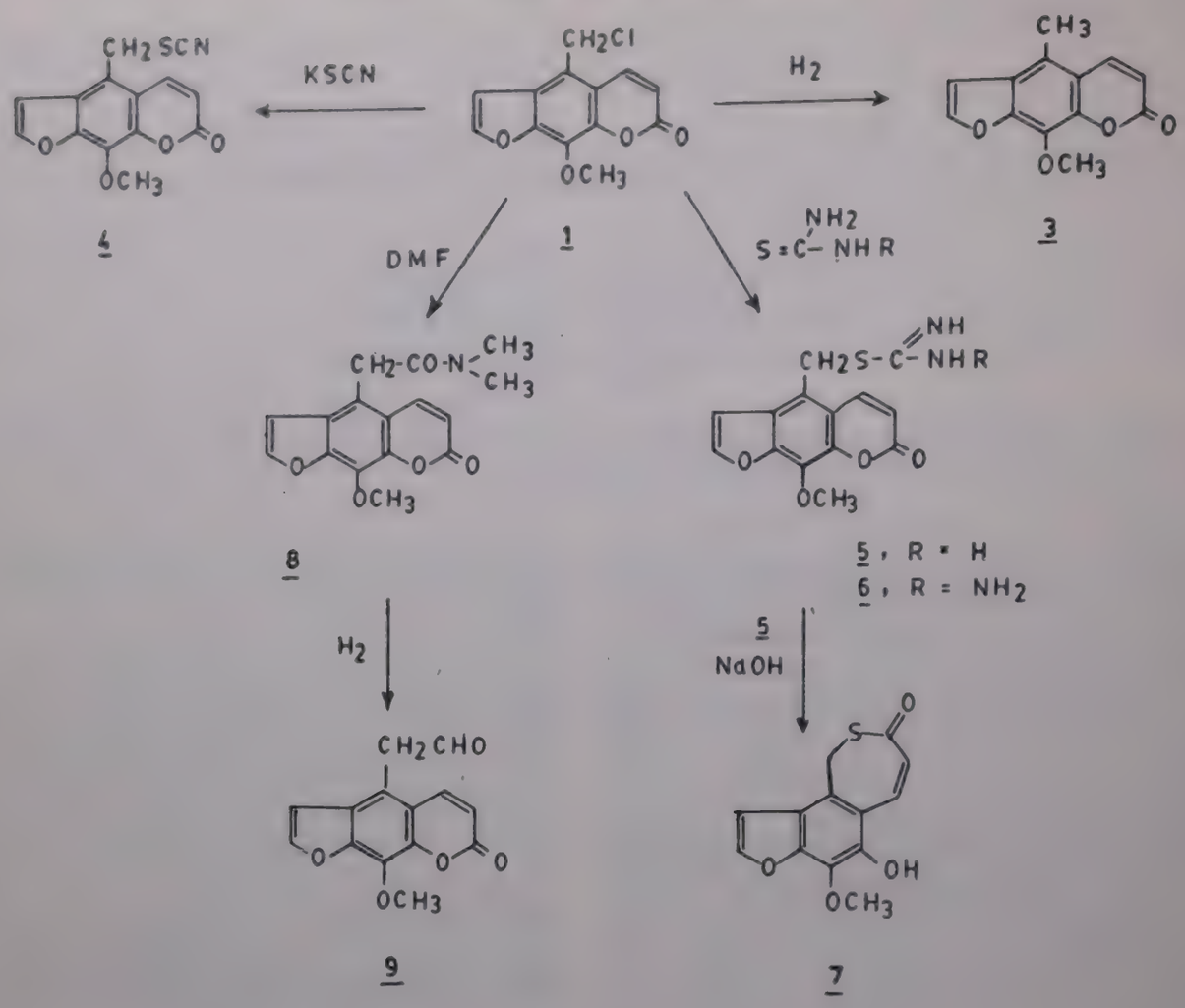


SCHEME 1

4-*Methylxanthotoxin* (**3**)

To a solution of chloromethylxanthotoxin (**1**, 2.6 g) in acetic acid (50 ml) was added zinc dust (10 g) and the mixture heated on a steam-bath for 5 hr. The reaction mixture was filtered, the zinc salt washed with little acetic acid and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in acetone, filtered, the acetone solution evaporated. On addition of methanol, the desired compound crystallized out, yield 50%, m.p. 185° (Found: C, 67.5; H, 4.4. $C_{13}H_{10}O_4$ requires C, 67.8; H, 4.3%).

4-*Cyanothiomethylxanthotoxin* (**4**)

To a solution of **1** (1.3 g) in 1:1 benzene-acetone (40 ml) was added potassium thiocyanate (0.5 g) and the mixture heated under reflux until KCl began to precipitate. Refluxing was continued for additional 30 min, filtered and the filtrate concentrated. The residue was crystallized from methanol to give white needles of **4**, yield 87%, m.p. 175° (Found: C, 59.1; H, 3.4; N, 4.6. $C_{14}H_9NO_4S$ requires C, 58.5; H, 3.1; N, 4.9%).

4-(*Amidinothiomethyl*)*xanthotoxin hydrochloride* (**5**)

To a solution of thiourea (0.8 g) in 1:1 benzene-acetone (50 ml) was added **1** (2.6 g) and the mixture refluxed on a water-bath for 2 hr. The product which separated out was filtered, washed with acetone, dried and crystallized from ethanol to give white plates of **5**, yield 100%, m.p. 220° (Found: C, 49.7; H, 4.2; N, 8.3. $C_{14}H_{13}N_2O_4SCl$ requires C, 49.3; H, 3.8; N, 8.2%).

4-(*Semicarbazidothiomethyl*)*xanthotoxin hydrochloride* (**6**)

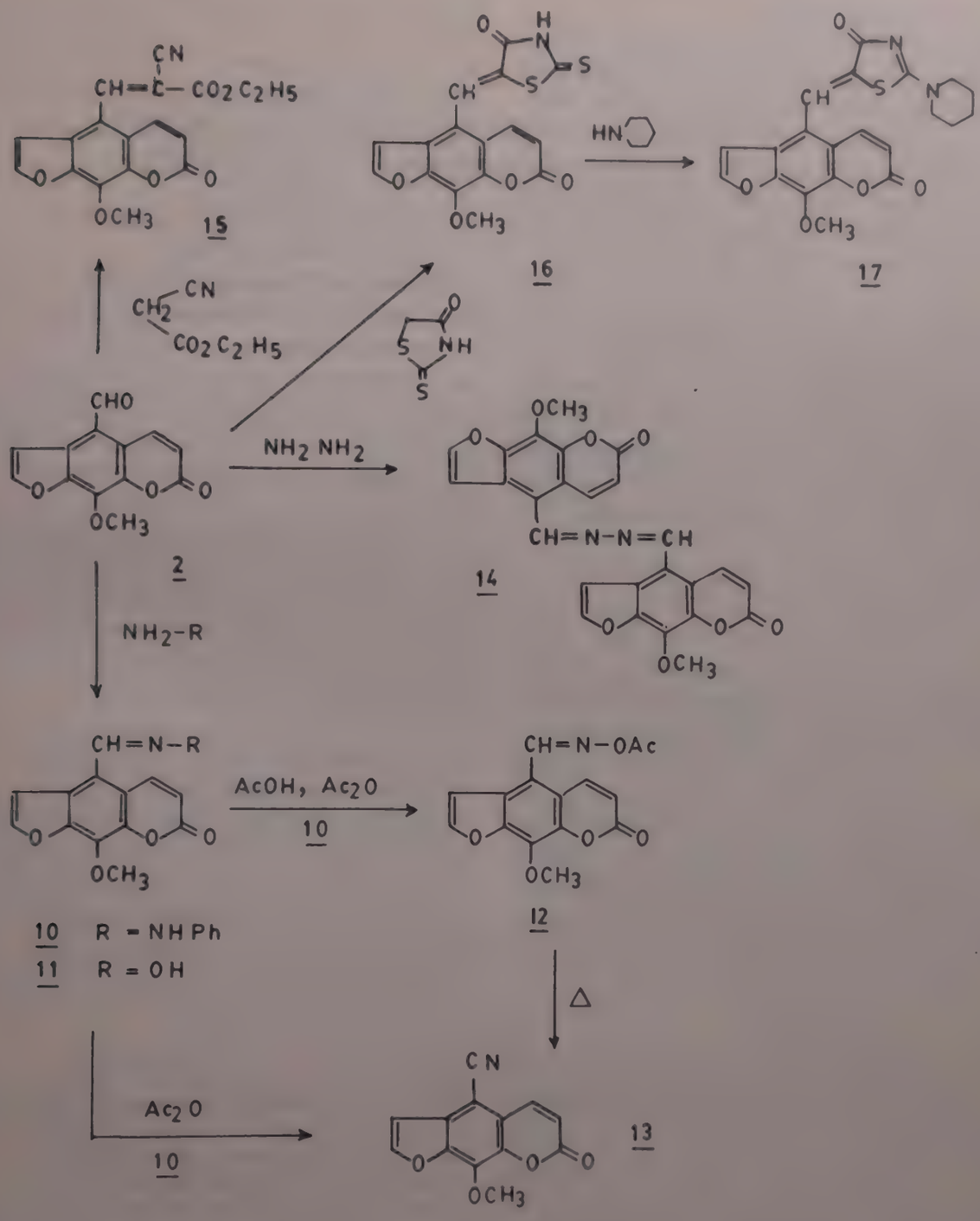
It was prepared as above using semicarbazide instead of thiourea. The product was crystallized from ethanol, yield 76%, m.p. 205° (Found: C, 47.2; H, 3.6; N, 12.1. $C_{14}H_{14}N_3O_4SCl$ requires C, 47.3; H, 3.9; N, 11.8%).

9-*Hydroxy*-10-*methoxy*-5-*thia*-6-*oxohept*-8-*eno*-[4,5-*c*]*benzofuran* (**7**)

A solution of **5** (0.5 g) in 10% aq. NaOH (15 ml) was heated on a steam-bath for 2 hr. The reaction mixture was cooled, acidified with dil. HCl, the solid filtered, washed with cold water and crystallized from dil. methanol, yield 62%, m.p. 190° (Found: C, 59.8; H, 3.7; S, 11.9. $C_{13}H_{10}O_4S$ requires C, 59.5; H, 3.8; S, 12.2%).

4-(*N,N-Dimethylacetamido*)*xanthotoxin* (**8**)

A mixture of **1** (2.6 g) and dimethylformamide (50 ml)



SCHEME 2

was heated on a steam bath for 3 hr, concentrated under reduced pressure to dryness and the product crystallized from ethanol, yield 88 %, m.p. 224° (Found: C, 63.4; H, 4.7; N, 4.3. $C_{16}H_{15}NO_5$ requires C, 63.8; H, 5.0; N, 4.6 %).

Xanthotoxin-4-acetaldehyde (**9**)

To a mixture of **8** (1.5 g) and ether (50 ml) was added a solution of $LiAlH_2(OC_2H_5)_2$ (prepared from 0.5 g $LiAlH_4$ and 1.9 ml ethanol) in ether (25 ml). The reaction mixture was kept overnight, filtered and the filtrate evaporated to dryness ,and the residue crystallized from methanol, yield 52 %, m.p. 236-37° (Found: C, 64.7; H, 4.1. $C_{14}H_{10}O_5$ requires C, 65.1; H, 3.9 %).

Xanthotoxin-4-formylhydrazobenzene (**10**)

A mixture of **2** (0.5 g), phenyl hydrazine hydrochloride (0.3 g) and anhydrous sodium acetate (0.3 g) in methanol (40 ml) was heated under reflux for 4-5 hr. The reaction mixture was concentrated, diluted with water, filtered and the residue crystallized from ethanol, yield 65 %, m.p. 211 (Found: C, 68.2; H, 4.5; N, 8.1. $C_{19}H_{14}N_2O_4$ requires C, 68.3; H, 4.2; N, 8.4 %).

Xanthotoxin-4-formaldehyde (**11**)

To a solution of **2** (1.2 g) in ethanol (25 ml) was added hydroxylamine hydrochloride (0.4 g) and anhydrous sodium acetate (0.5 g) and the mixture heated under reflux for 12 hr. The reaction mixture was concentrated, diluted with water, the solid filtered off, washed with water, dried and crystallized from ethanol, yield 67%, m.p. 259° (Found: C, 59.8; H, 3.6; N, 5.1. $C_{13}H_9NO_5$ requires C, 60.2; H, 3.5; N, 5.4%).

Xanthotoxin-4-formyloxime acetate (**12**)

A mixture of **11** (0.5 g), acetic anhydride (5 ml) and acetic acid (5 ml) was warmed gently on a water-bath when the desired acetate soon separated out. It was filtered, washed with cold water, dried and crystallized from methanol, yield 100%, m.p. 205° (Found: C, 60.1; H, 3.8; N, 4.6. $C_{15}H_{11}NO_6$ requires C, 59.8; H, 3.6; N, 4.6%).

4-*Cyanoxanthotoxin* (**13**)

Method A: Compound (**11**, 0.5 g) and acetic anhydride (5 ml) was heated under reflux for 1 hr, cooled and poured on to crushed ice. The separated solid was filtered off, washed with water, dried and crystallized from methanol to give **13**, yield 92%, m.p. 255°.

Method B: The aldoxime acetate (**12**, 0.5 g) was heated on an oil-bath till it melted. This molten product which soon solidified was heated for 30 min, cooled and crystallized from methanol, yield 91%, m.p. 255° (Found: C, 65.2; H, 3.0; N, 5.7. $C_{13}H_{11}NO_4$ requires C, 64.7; H, 2.9; N, 5.8%).

Xanthotoxin-4-formylazine (**14**)

A mixture of **2** (0.5 g), hydrazine hydrate (0.4 ml) and anhydrous sodium acetate (0.3 g) in ethanol (20 ml) was heated under reflux for 2 hr during which an orange precipitate separated out. This was filtered, successively washed with a little ethanol, water and ethanol and dried, yield 82%, m.p. >360° (Found: C, 64.7; H, 3.2; N, 6.1. $C_{26}H_{16}N_2O_8$ requires C, 64.5; H, 3.3; N, 5.8%).

4-(1-*Cyano-1-ethoxycarbonylethylen-2-yl*)-*xanthotoxin* (**15**)

A mixture of **2** (1.2 g), ethyl cyanoacetate (0.7 ml) and triethylamine (0.1 ml) in ethanol (50 ml) was heated under reflux for 15 hr. The clear solution was concentrated to quarter its volume, allowed to cool when a solid product crystallized out, yield, 58%, m.p. 220° (Found: C, 63.5; H, 4.0; N, 4.4. $C_{18}H_{13}NO_6$ requires C, 63.7; H, 3.8; N, 4.1%).

4-[(4-*Oxo-2-thioxo-1,3-thiazolidin-5-yl*)-*methyleno*]*xanthotoxin* (**16**)

Method A: Compound (**2**, 1.2 g), rhodanine (0.7 g) and anhydrous sodium acetate (0.6 g) in acetic acid (10 ml) were heated under reflux for 2 hr. The mixture was concentrated under reduced pressure to half its volume and allowed to cool. The product that crystallized out was filtered, washed several times with water dried and crystallized from acetic acid, yield 100%, m.p. 283°.

Method B: A solution of **2** (0.5 g), rhodanine (0.3 g), and triethylamine (0.1 ml) in ethanol (20 ml) was heated under reflux for 2-3 hr. The separated product was filtered and crystallized from ethanol, yield 98%, m.p. 283° (Found: C, 53.5; H, 2.7; N, 3.7. $C_{16}H_9NO_5S_2$ requires C, 53.5; H, 2.5; N, 3.9%).

4-[(4-*Oxo-2-piperidino-1,3-thiazol-5-yl*)-*methyleno*]*xanthotoxin* (**17**)

The rhodanine base (**16**, 0.5 g), piperidine (0.5 ml) and *n*-butanol (25 ml) were heated under reflux for 3-4 hr (until no more H_2S evolved). The reaction mixture was cooled, the crystallized product filtered and recrystallized from ethanol, yield 78%, m.p. (Found: C, 61.0; H, 4.2; N, 6.5. $C_{21}H_{18}N_2O_5S$ requires C, 61.5; H, 4.4; N, 6.8%).

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Claisen Condensation of Diacetylmonohydroxy- & Diacetyldihydroxy- chromans: Synthesis of Some New Chromones & a Bischromone

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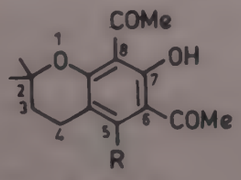
Claisen condensation of 6,8-diacetyl-7-hydroxy-2,2-dimethylchroman (I) with ethyl acetate and sodium gives the isomeric chromones, 10-acetyl-2,2,8-trimethyl-3,4-dihydro-2*H*,6*H*-benzo[1,2-b : 5,4-b′]dipyran-6-one (II) and 6-acetyl-2,2,8-trimethyl-3,4-dihydro-2*H*,10*H*-benzo[1,2-b : 3,4-b′]dipyran-10-one (III). A similar reaction of 6,8-diacetyl-5,7-dihydroxy-2,2-dimethylchroman (IV) affords three products identified as 6-acetyl-5-hydroxy-2,2,8-trimethyl-3,4-dihydro-2*H*,10*H*-benzo[1,2-b : 3,4-b′]dipyran-10-one (V), 10-acetyl-5-hydroxy-2,2,8-trimethyl-3,4-dihydro-2*H*,6*H*-benzo[1,2-b : 5,4-b′]dipyran-6-one (VII) and 2,2,6,10-tetramethyl-3,4-dihydro-2*H*,8*H*,12*H*-benzo[1,2-b : 3,4-b′ : 5,6-b″]tripyran-8,12-dione (VIII). Compounds V and VII on reaction with ethyl acetate and sodium give VIII and 10-acetoacetyl-5-hydroxy-2,2,8-trimethyl-3,4-dihydro-2*H*,6*H*-benzo[1,2-b : 5,4-b′]dipyran-6-one (IX) respectively. Further, compound VII has been dehydrogenated to 10-acetyl-5-hydroxy-2,2,8-trimethyl-2*H*,6*H*-benzo[1,2-b : 5,4-b′]dipyran-6-one (XI).

We have,earlier reported the synthesis of dihydropyranochromones by the Claisen condensation of appropriately substituted *o*-hydroxyacetylchromans with ethyl acetate and sodium[1]. The Hoesch acetylation of 7-hydroxy-2,2-dimethylchroman and 5,7-dihydroxy-2,2-dimethylchroman with acetonitrile and hydrogen chloride[2] gave in addition to the monoacetyl derivatives, the diacetyl products I and IV. These on Claisen condensation can undergo cyclisation in more than one way and a mixture of products may therefore be expected to be formed. The present paper describes the results of our studies on the reactions of I and IV with ethyl acetate and sodium and the characterisation of the products by chemical transformation and spectral data.

Chroman I can give rise to the linear and angular chromones (II and III) while chroman IV can yield the possible products V-VIII. On Claisen condensation of I, both the possible products II and III were obtained and were separated by chromatography over silica gel.



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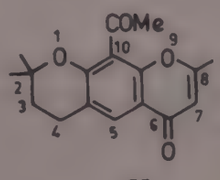
IV R = OH



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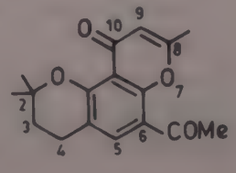

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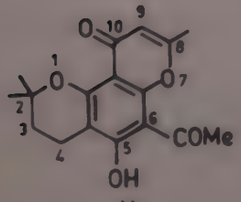

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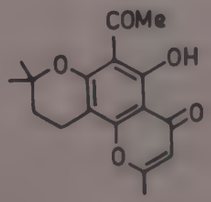

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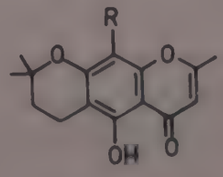
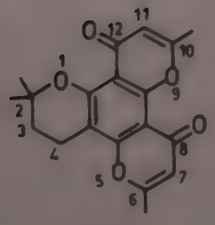
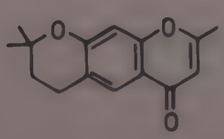


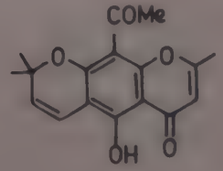
VII R = COMe
IX R = $COCH_2COMe$



VIII



X



XI

The UV spectrum of one of the products was similar to that of the linear chromone X and hence this product was assigned the structure II. Consequently, the other product was formulated as III.

Chroman IV on similar reaction gave three products C, D and E. On further condensation with ethyl acetate and sodium, C yielded a product identical with the bischromone VIII. Structure VII was therefore excluded for C since it cannot form VIII. Between the two possible structures V and VI, C was assigned the structure V on the basis of PMR spectral data and comparison with compound VII. For the diacetylchroman[3] (IV), the signals due to the C-7 and C-5 phenolic protons appeared at δ 16.05 and 15.03 respectively, the former being more dishielded than the latter due to two *o*-acetyl groups. In V and VI too, the phenolic protons must be unequally deshielded. The signal at δ 13.10 may reasonably be attributed to the less deshielded C-5 hydroxyl proton and hence the C-7 hydroxyl is concluded to be involved in cyclisation. In V and VII, the hydroxyl groups are similarly placed and the signal for the phenolic proton of VII at δ 13.24 is comparable with that of C at δ 13.10. Based on these observations, product C was assigned the structure V. Benzylic bromination of VII with N-bromosuccinimide followed by dehydrobromination with pyridine afforded XI.

Compound D on further reaction with ethyl acetate and sodium gave a product which analysed for $C_{19}H_{20}O_6$ and showed IR absorption bands at 1675, 1625 (β-diketone) cm^{-1}. The acetyl group of D was presumably converted into the acetoacetyl group to give product IX. Structure VII was therefore assigned to D.

Compound E analysed for $C_{19}H_{18}O_5$ and did not give coloration with alcoholic ferric chloride. The PMR spectral data confirmed this compound to be the bischromone VIII.

Experimental Procedure

Melting points are uncorrected. IR spectra were recorded in nujol on Perkin-Elmer 237 spectrometer, UV spectra in MeOH on a Varian Superscan-3 spectrophotometer and PMR spectra in $CDCl_3$ on a Varian XL-100 spectrometer (100 MHz) using TMS as internal standard.

Claisen condensation of chroman I with ethyl acetate and sodium

A solution of I (0.52 g) in dry ethyl acetate (6 ml) was added to pulverised sodium (0.6 g) with shaking and the mixture allowed to stand in the cold for 48 hr. The residue obtained after removal of excess ethyl acetate under reduced pressure was treated with crushed ice and hydrochloric acid. The precipitated solid was filtered, dissolved in ethanol containing a trace of conc. sulphuric acid and heated under reflux for 30 min. The solution was concentrated to remove most of the ethanol and the residual mixture diluted with water to yield a solid. Column chromatography of the solid over silica gel and elution with hexane-ethyl acetate (80 : 20) gave II closely followed by III. Their characterisation data are as follows:

10-Acetyl-2,2,8-trimethyl-3,4-dihydro-2H, 6H-benzo[1,2-b : 5,4-b′}dipyran-6-one (II)

It crystallised from hexane-ethyl acetate as colourless prisms, yield 0.26 g, m.p. 137-38°; IR: 1660, 1655 cm^{-1}; UV: 224 (log ε 4.02), 253 (3.82), 305 (3.90) nm; PMR: δ 1.42 (*s*, 6H, *gem*-dimethyl), 1.90 (*s*, 2H, 3-CH_2, $J = 7$Hz), 2.18 (*s*, 3H, C_8-CH_3), 2.38 (*s*, 3H, $C_{10}-COCH_3$), 2.94 (*s*, 2H, 4-CH_2, $J = 7$ Hz); 5.94 (*s*, 1H, C_7-H), 7.94 (*s*, 1H, C_5-H) (Found: C, 71.1; H, 6.2. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.3%).

6-Acetyl-2,2,8-trimethyl-3,4-dihydro-2H, 10H-benzo[1,2-b : 3,4-b′]dipyran-10-one (III)

It crystallised from hexane-ethyl acetate as fine needles, yield 0.12 g, m.p. 155-57°; IR: 1665, 1655 cm^{-1}, UV: 210 (log ε 3.82), 261 (3.74), 312 (3.82) nm; PMR: δ 1.44 (*s*, 6H, *gem*-dimethyl), 1.88 (*t*, 2H, 3-CH_2, $J = 7$ Hz), 2.20 (*s*, 3H, C_8-CH_3), 2.38 (*s*, 3H, C_6-COCH_3), 2.92 (*t*, 2H, 4-CH_2, $J = 7$ Hz), 6.02 (*s*, 1H, C_9-H), 7.92 (*s*, 1H, C_5-H) (Found: C, 71.0; H, 6.5. $C_{17}H_{18}O_4$ requires: C, 71.3; H, 6.3%).

Claisen condensation of chroman IV with ethyl acetate and sodium

The chroman IV (2.08 g) in dry ethyl acetate (25 ml) was added to pulverised sodium (2.20 g) and the reaction mixture kept in the cold for 72 hr and worked-up. The crude product showed three components on TLC and these were separated by column chromatography over silica gel. Elution with hexane-ethyl acetate mixtures (i) 92 : 8, (ii) 90 : 10 and (iii) 88 : 12 furnished the products V, VII and VIII respectively. Their characterisation data are as follows:

6-Acetyl-5-hydroxy-2,2,8-trimethyl-3, 4-dihydro-2H,10H-benzo[1,2-b : 3,4-b′]-dipyran-10-one (V)

It crystallised as white prisms from hexane-ethyl acetate, yield 0.30 g, m.p. 172-73°, gave bluish-violet ferric coloration; IR: 1695, 1660 cm^{-1}; UV: 204 (log ε 3.75), 234 (3.77), 258 (3.75), 295 (4.40) nm; PMR: δ 1.40 (*s*, 6H, *gem*-dimethyl), 1.84 (*t*, 2H, 3-CH_2, $J = 7$ Hz), 2.38 (*s*, 3H, C_8-CH_3), 2.48 (*s*, 3H, C_6-COCH_3), 2.74 (*t*, 2H, 4-CH_2, $J = 7$ Hz), 5.94 (*s*, 1H, C_9-H), 13.10 (*s*, 1H, C_5-OH) (Found: C, 67.8; H, 5.8. $C_{17}H_{18}O_5$ requires C, 67.5; H, 6.0%).

10-Acetyl-5-hydroxy-2,2,8-trimethyl-3,4-dihydro-2H,6H-benzo[1,2-*b*:5,4-*b'*]-*dipyran-6-one* (*VII*)

It crystallised as colourless prisms from hexane-ethyl acetate, yield, 0.60 g, m.p. 200-201°; gave bluish-violet ferric coloration; IR: 1680, 1650 cm^{-1}; UV: 206 (log ε 4.4), 229 (4.16), 266 (4.28), 280 (4.16) nm; PMR: δ 1.44 (*s*, 6H, *gem*-dimethyl), 1.84 (*t*, 2H, 3-CH_2, $J=7$ Hz), 2.36 (*s*, 3H, C_8-CH_3), 2.66 (*t*, 2H, 4-CH_2, $J=7$ Hz), 2.76 (*s*, 3H, $C_{10}-COCH_3$), 5.98 (*s*, 1H, C_7-H), 13.24 (*s*, 1H, C_5-OH) (Found: C, 67.7; H, 6.0. $C_{17}H_{18}O_5$ requires C, 67.5; H, 6.0%).

2,2,6,10-*Tetramethyl*-3,4-*dihydro*-2*H*,8*H*,12*H*-*benzo*[1,2-*b*:3,4-*b'*:5,6-*b''*]*tripyran*-8,12-*dione* (*VIII*)

It crystallised as colourless prisms from hexane-ethyl acetate, yield 0.52 g, m.p. 178-79°, gave negative ferric reaction; IR: 1665, 1660 cm^{-1}; UV: 203 (log ε 3.76), 231 (3.55), 263 (3.84), 304 (3.25), nm; PMR: δ 1.42 (*s*, 6H, *gem*-dimethyl), 1.87 (*t*, 2H, 3-CH_2, $J=7$ Hz), 2.38, 2.54 (*s*, each, 6H, C_6-CH_3 and $C_{10}-CH_3$), 2.74 (*t*, 2H, 4-CH_2, $J=7$ Hz), 5.98, 6.02 (*s*, each, 2H, C_7-H and $C_{11}-H$) (Found: C, 70.0; H, 5.3. $C_{19}H_{18}O_5$ requires C, 69.9; H, 5.5%).

Product VIII was also obtained as follows: The chromone V (0.30 g) in dry ethyl acetate (3.0 ml) was added to pulverised sodium (0.30 g) and the reaction mixture kept in the cold for 72 hr and worked-up. The crude product was purified on a silica gel column using hexane-ethyl acetate (88:12) as eluent and crystallised from the same solvent mixture to give VIII as colourless prisms, yield, 0.14 g, m.p. and m.m.p. 177-79° (superimposable IR spectra).

Claisen condensation of VII with ethyl acetate and sodium: Formation of 10-acetoacetyl-5-hydroxy-2,2,8-trimethyl-3,4-dihydro-2H,6H-benzo[1,2-*b*:5,4-*b'*]-*dipyran-6-one* (*IX*)

A solution of VII (0.30 g) in dry ethyl acetate (3.0 ml) was added to pulverised sodium (0.30 g) and the reaction mixture kept in the cold for 72 hr and worked-up. The crude product after purification on a silica gel column using hexane-ethyl acetate (85:15) as eluent was crystallised from the same solvent to give colourless prisms, yield, 0.13 g, m.p. 155-56°; IR: 1675, 1665, 1625, 1575 cm^{-1} (Found: C, 66.1; H, 5.7. $C_{19}H_{20}O_6$ requires C, 66.3; H, 5.9%).

Dehydrogenation of VII: Formation of 10-acetyl-5-hydroxy-2,2,8-trimethyl-2H,6H-benzo[1,2-*b*:5,4-*b*]*dipyran-6-one* (*XI*)

A mixture of VII (0.30 g), N-bromosuccinimide (0.20 g) and dibenzoyl peroxide (10 mg) in carbon tetrachloride (20 ml) was refluxed for 3 hr, cooled and the succinimide filtered off. The residue obtained after removal of solvent was heated to reflux with pyridine (3 ml) for 2 hr. Pyridine was removed under reduced pressure and the residue purified on a silica gel column using hexane-ethyl acetate (88:12) as eluent to give IX which crystallised from the same solvent as pale yellow prisms, yield 0.15 g, m.p. 240-41°; IR: 1675, 1650 cm^{-1}; PMR: δ 1.42 (*s*, 6H, *gem*-dimethyl), 2.26 (*s*, 3H, C_8-CH_3), 2.42 (*s*, 3H, $C_{10}-COCH_3$), 5.68 (*d*, 1H, C_3-H, $J=10$Hz), 5.92 (*s*, 1H, C_7-H), 6.40 (*d*, 1H, C_4-H, $J=10$Hz), 13.18 (*s*, 1H, C_5-OH) (Found: C, 68.1; H, 5.6. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%).

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Infrared Group Frequencies of α-Methylene-γ-lactone Grouping in *cis*- & *trans*-Eudesmanolides, Germacranolides, Eleminic Lactones & Guianolides

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Detailed IR spectral study of a large number of α-methylene-γ-lactones and their saturated analogues shows that the α-methylene-γ-lactone moiety is completely characterisable by IR spectra. The band due to one of the νC−O skeletal modes (1250-1275 cm^{-1}) shows discernable difference in frequency between *cis*- and *trans*-eudesmanolides. The other νC−O skeletal mode (1130 cm^{-1}) is sensitive to the conformational effects brought about by small structural variations in an otherwise same carbocyclic system and many times appears with distinct modifications.

Sesquiterpene α-methylene-γ-lactones are among the most widely distributed terpenoids, known for their structural complexity and diversity of skeletal types[1,2]. Their tumour inhibitory activity[3], stemming from the α-methylene-γ-lactone grouping, has given an added impetus to their isolation and synthesis.

The present study aims at a systematic analysis of the group frequencies of the α-methylene-γ-lactone moiety in a large number of *cis*- and *trans*-eudesmanolides (**1-12**), germacranolides (**13**, **14**) and guianolides (**17**, **18**) for its ready identification by IR spectroscopy. Besides, the possibility of predicting the stereochemistry of the lactone ring fusion by observing any systematic variation or modification of any of the group frequencies has been explored.

Materials and Methods

All the spectra were taken on a Perkin-Elmer grating infrared spectrophotometer model 237 B with polystyrene as the internal standard. In the region 4000-1400 cm^{-1} the spectra were taken in carbon tetrachloride (AR) while in the region 1400-675 cm^{-1} in carbon disulphide in a 1 mm cell, except otherwise stated. All the compounds were freshly recrystallised and their preparations appear elsewhere.

Results and Discussion

C=O stretching vibration†

This band appears at or around 1775 (CCl_4), and shows a frequency decrease of 5-15, from that of their saturated analogues (Table 1). This is a general feature of *cis*-conjugation even in strainless systems[4]. The appearance of νC=O as compared to that of the ester, is due to strain and many theories exist as to its mode of operation[5].

Esters are known to exist[5] in a conformation in which the O−R eclipses the C=O (Fig. 1), and among other factors we feel that the greater conjugation possible between the lone-pair orbitals and C=O might actuate this preference. This preferred conformation is radically disturbed in a γ-lactone ring with the resultant effect of the lone-pair orbital being directed *cis* to that of C=O (Fig. 1). This might prevent effective conjugation with carbonyl, affecting the C=O dipole and hence frequency.

Methyl acrylate (**20**) shows[4] only a single band due to the νC=O although the cisoid and transoid forms co-exist at room temperature. There is a considerable

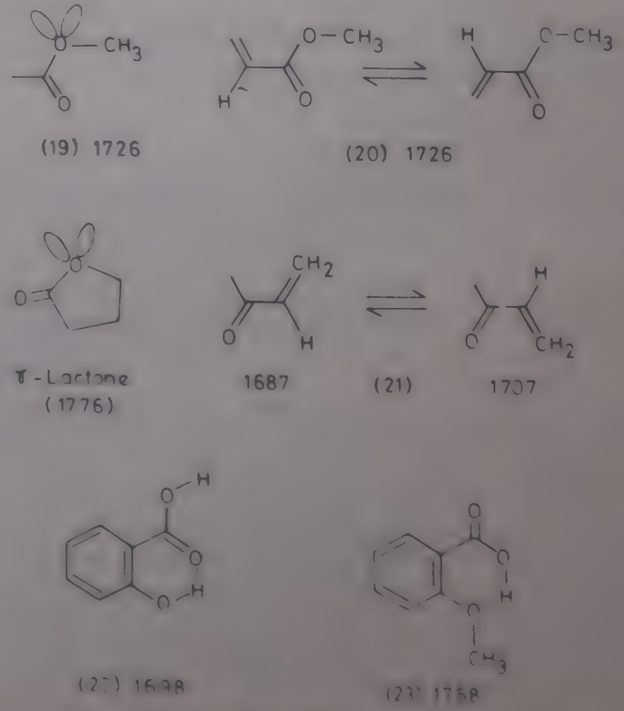
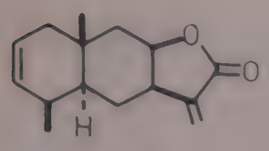


Fig. 1 — Frequencies of carbonyl absorption in **19-23**

†IR ν_{max} in cm^{-1} throughout the paper



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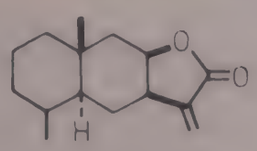

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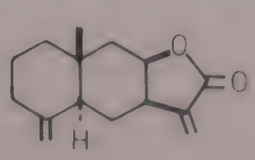

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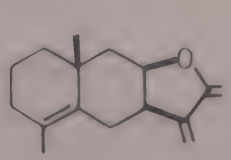

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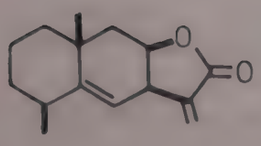

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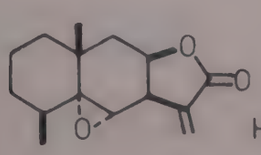

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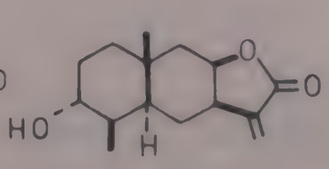

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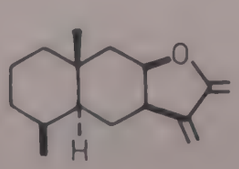

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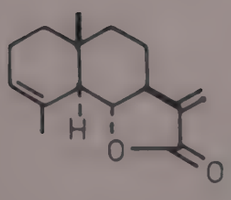

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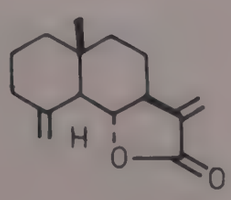

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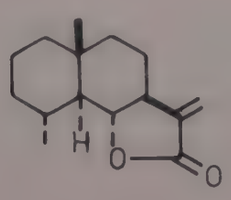

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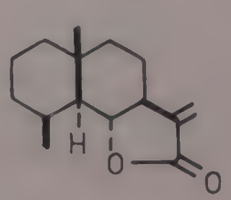

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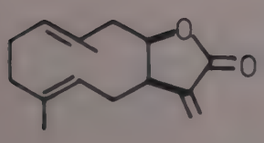

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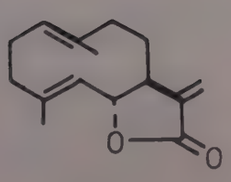

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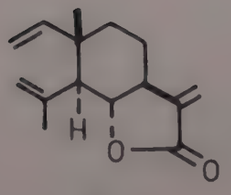

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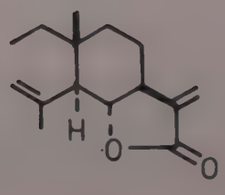

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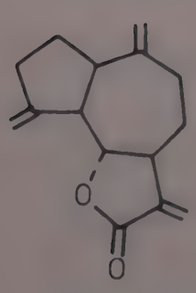

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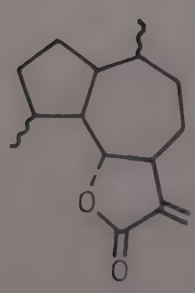

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frequency difference between the hydrogen bonded forms of **22**[5] and **23**[5]. These further serve to illustrate the role of lone-pair orbitals in frequency determination in esters, lactones and acids.

Intensity of carbonyl absorption

The *cis*-eudesmanolides (**1-8**) exhibit[6] greater E^a values than the *trans*-eudesmanolides (**9-12**). This is due to the fact that the strain endengered at B/C junction due to B/C torsional incompatibility is accommodated by a slight flattening of ring-B itself in *cis*-fused systems[7]. The *trans*-coupling of ring-B with the naturally flattened ring-C causes the opening of the dihedral angles along the C_6-O, C_7-C_{11} planes, which in turn disturb the planarity of the conjugated system due to rotation around the $C_{11}-C_{13}$ bond in the process of a strain transmission. Significantly, the UV spectrum of the *cis*-lactone (**8**) $\lambda_{max} = 219$ nm, $E^a = 5960$ shows a higher E^a value than the *trans*-lactone (**12**, $\lambda_{max} = 217$ nm, $E^a = 5660$), a pair of lactones especially chosen to avoid the complicating effects of unsaturation elsewhere in the system. Braude's type I steric effect[5] typically holds good here.

Compounds containing the α-methylene-γ-lactone

Table 1 — Group Frequencies of α-Methyelene-γ-lactone Moiety in (1-18)

Compd	νC=O	νC=C	δC=CH₂ (in-plane)	νC-O (skeletal)	νC−O (skeletal)	δ=CH₂ (out-of plane)	Skeletal mode
1	1762 (1017)	1655 (w)	–	1260 (274)	1140 (315) 1165 (326)	935 (198)	810 (85)
2	1767 (997)	–	–	1265 (286)	1130 (233) 1150 (141)	930 (172)	810 (97)
3	1782 (907)	1165 (37)	1415 (70)	1265 (430)	1132 (581)	935 (255)	815 (148)
4	1767 (1011)	–	–	1255 (410)	1110 (270) 1130 (Sh) 1145 (Sh)	930 (214)	800 (110)
5	1780 (1021)	1660 (29)	1407 (36)	1270 (533)	1136 (177) 1127 (324) 1162 (152)	937 (216)	815 (72)
6	1770 (1001)	–	–	1270 (294)	1132 (417) 1160 (114)	945 (152)	816 (114)
7	1768 (978)	–	–	1260	1148 1115	935	810
8	1780 (1009)	1662 (30)	1420 (w) 1430 (w)	1265 (430)	1130 (371) 1155 (396)	935 (173)	818 (130)
9	1385 (767)	1670 (32)	1415 (69)	1250 (335)	1135 (301) 1120 (275)	936 (338)	815 (91)
10	1780 (766)	–	–	1250 (183) 1260 (151) 1275 (151)	1130 (324) 1150 (129)	940 (301)	818 (123)
11	1780 (834)	1672 (w)	1415 (83)	1250 (304)	1137 (348)	940 (297)	816 (90)
12	1778 (833)	1675 (w)	1415 (85)	1250 (283)	1134 (416)	937 (317)	816 (114)
13	1770 (708)	1662 (w)	1401 (44)	1267 (215)	1134 (257)	939 (200)	812 (139)
14	1775 (942)	1670 (95)	1405 (74)	1140 (524)	1250 (403)	940 (294)	815 (112)
15	1780 (838)	1675 (25)	1415 (84)	1255 (213) 1248 (sh) 1240 (sh)	1140 (244)	940 (306)	816 (107)
16	1782 (908)	1675 (30)	1402 (50) 1418 (61)	1253 (177) 1243 (177)	1130 (267) 1148 (sh)	935 (298)	812 (110)
17	1780 (1036)	1670 (–)	1407 (87)	1260 (324)	1150 (231) 1130 (133)	942 (264)	815 (120)
18	1778 (1352)	1670	–	1262 (162) 1250 (sh)	1151 (144) 1135 (93) 1125 (139)	940 (221)	815 (86)

moiety as the only reactive function exhibit by far the most uniform band shapes for the carbonyl absorption. The less polar solvents give rise to much sharper bands than the more polar solvents. In chloroform the bands shift by about 10 cm^{-1} compared to its position in carbon tetrachloride. Many lactones, particularly those which have an exomethylene group at C-4, exhibit irregular band contours[9] and these should be possibly traced to Fermi resonance.

All lactones exhibit a clear overtone due to $\nu C=O$ at about double the fundamental frequency.

C—O skeletal stretching vibrations

All α-methylene-γ-lactones exhibit two principal bands in the region 1100-1300, due to skeletal $\nu C-O$. One of these bands occurring between 1250-1275 is sharp with medium intensity. In all the *trans*-eudesmanolides (**9-12**) the band appears at 1250, whereas in the *cis*-eudesmanolides (**1-8**) around 1270. In the *trans*-germacranolide (**14**)[10], the band appears at 1250 whereas in the *cis*-germacranolide (**13**)[11] it appears at 1270. This band is sharp and well-defined in all lactones except in **10**, **15** and **16**, wherein the differential field influence of the methylene group on the ethereal oxygen atom, either splits or introduces flexing. This band disappears in the corresponding $C_{11}-C_{13}$ dihydro-derivatives and several bands of insignificant intensities appear in this region.

The other $\gamma C-O$ skeletal mode occurring around 1130 is sensitive to even small structural variations in otherwise same carbocyclic systems and many times appears with distinctive split patterns, and is generally indicative of the degree of conformational mobility in these systems. In general, any strain in the rest of the carbocyclic system is immediately reflected in the nature of the absorption in this region.

Among *cis*-eudesmanolides, **3** and **6** show a single band at 1132, while **5** carrys a distinct shoulder at 1136 on the principal band at 1127. While lactone (**8**) shows two equal intensity bands at 1130 and 1155, lactone (**1**) shows a principal band at 1130 besides a band of weaker intensity at 1150. Lactone (**7**) shows a principal band at 1148 besides a weaker band at 1110 with shoulders at 1130 and 1145.

Among the *trans*-eudesmanolides the *endo* and *exo* double bonds in ring-A and **9** and **10** cause different splitting patterns in the region around 1130. However, when ring-A is saturated, as in **11** and **12**, only a single band appears at 1134 and 1137, respectively (Table 1).

Both the germacranolides (**13**) and (**14**) show a single band at 1130 and 1140 respectively. In the eleminic lactones (**15**) and (**16**) the band is broadened with indistinct splits. In both the guianolides (**17**) and (**18**) multiple bands are seen in this region.

In the saturated analogues of the parent α-methylene-γ-lactones several bands appear between 1100 and 1200. In general the *cis*-eudesmanolides and germacranolides exhibit a better pattern than *trans*-eudesmanolides, guianolides and elemenic lactones.

Out-of-plane bending vibration of conjugated exomethylene group

The band due to δCH_2 (out-of-plane) is extremely characteristic and appears[12] as a single band in all lactones at about 935. Even in methyl methacrylate, the band appears ~940, the high frequency being due to resonance factors[13].

Unlike the out-of-plane vibration, the δCH_2 in-plane vibration does not shift and appears around 1420. In some lactones this band overlaps with a nonconjugated exomethylene group.

All the conjugated lactones exhibt a rather weak band due to exomethylene stretching vibration around 1670.

A band around 820 is seen in all conjugated lactones whose origin is uncertain[12]. This band is also observed in methyl methacrylate[13].

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Synthesis & Reactions of Some 4-Oxo-4*H*-1-benzopyran-2-carboxaldehydes

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Some new 4-oxo-4*H*-1-benzopyran-2-carboxyldehydes (III) have been prepared, and the conversion of the 2-carboxaldehyde group in III into 2-carbonitrile and 2-carboxylic acid groups has been discussed. Unlike the general behaviour of the 4-oxo-4*H*-1-benzopyrans towards some nucleophiles, where the reaction takes place with opening of the pyronering, the 6-methyl- and 6-chloro-4-oxo-4*H*-1-benzopyran-2-carboxaldehydes (IIIa and IIIb) have been found to react with different nucleophiles such as hydroxylamine hydrochloride, hydrazine, phenylhydrazine and primary aromatic amines to give the corresponding condensation products (IV, VII, VIII, X, XI) without the opening of pyrone ring. The only exception to this observation is the reaction of IIIa and IIIb with ethylene diamine where the opening of pyronering does not take place to give the expected 5,6-dihydropyrazine derivatives (XIIa and XIIb). The reactions of IIIa and IIIb with active methylene compounds, malonic acid, malonodinitrile, cyanoacetic acid, ethyl cyanoacetate, cyanoacetamide and hippuric acid have also been discussed.

Curreltly 4-oxo-4*H*-1-benzopyran-3-carboxaldehydes have generated much interest on account of their biological activities and several reports have appeared on their synthesis and reactions. However, the work on 4-oxo-4*H*-1-benzopyran-2-carboxaldehydes is very scanty[1]. In view of this we undertook the title investigation.

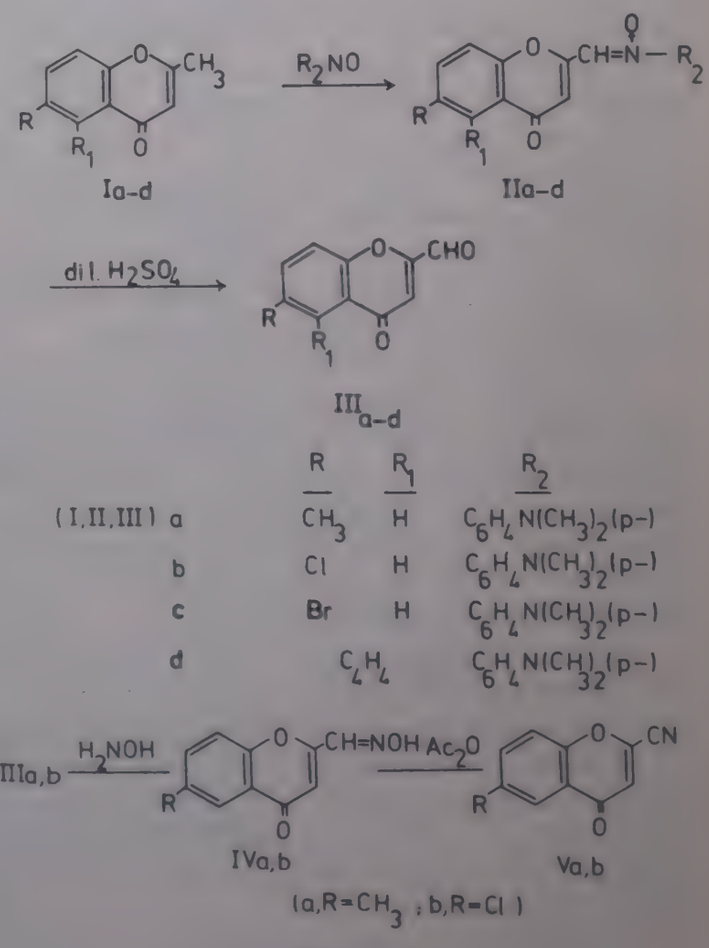
The new 4-oxo-4*H*-1-benzopyran-2-carboxaldehydes (III) were prepared by an indirect conversion of the 2-methyl group in 2-methyl-4-oxo-4*H*-1-benzopyrans (I) into carboxaldehyde function by a two-step reaction. The first step involved conversion of I into the corresponding nitrones (IIa-d) which on treatment with dil. sulphuric acid in the second step gave the desired carboxaldehydes (IIIa-d; Scheme 1).

The IR spectra of II displayed bands at 1640-1635 (pyrone CO) and 1610-1605 cm^{-1} (C=N). Compounds III in their IR spectra showed bands at 1720-1715 (CHO) and 1650-1655 cm^{-1} (pyrone CO). The PMR spectrum of IIIa, as a representative, exhibited signals at δ 9.8 (1H, *s*, CHO), 7.9 (1H, *s*, H-5), 7.71 (2H, *d*, *J* = 8 Hz, H-7 and H-8), 7.1 (1H, *s*, H-5) and 2.5 (3H, *s*, CH_3).

The reaction of IIIa,b with hydroxylamine hydrochloride is reported to bring about opening of the pyrone ring to give isoxazole derivatives[2,3].

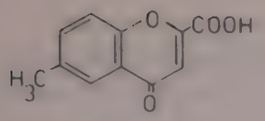
However, in the present study we have found that both IIIa and IIIb react with hydroxylamine hydrochloride in pyridine, ethanol or ethanol in the presence of hydrochloric acid to give the oximes IVa and IVb respectively (Scheme 1).

These oximes (IVa,b) when refluxed with acetic anhydride underwent dehydration giving the corresponding carbonitriles (Va and Vb) which were prepared earlier by Ellis[4] via the dehydration of 6-methyl- and 6-chloro-4-oxo-4*H*-1-benzopyran-2-carboxamides

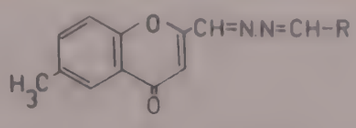


SCHEME 1

Zagorevskii *et al.*[5] have prepared 4-oxo-4*H*-1-benzopyran-2-carboxylic acids by the Claisen condensation of 2-hydroxyacetophenones with ethyl oxalate. Following this method, 6-methyl-4-oxo-4*H*-1-benzopyran-2-carboxylic acid (VI) was prepared. This

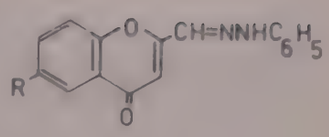


VI



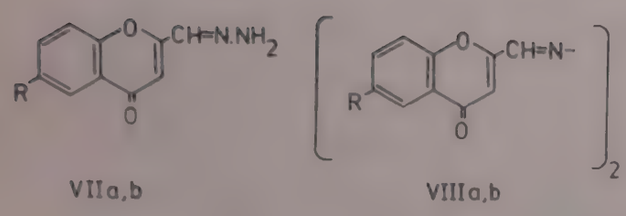
IX

	R
IXa	$C_6H_4OCH_3$ (p-)
b	C_6H_4Cl (o-)



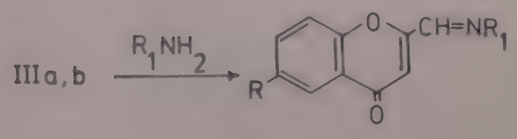
X

	R
X a	CH_3
b	Cl



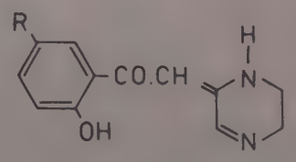
VIIa,b VIIIa,b

(a, R=CH_3 ; b, R=Cl)



XI

	R	R_1
XI a	CH_3	1-$C_{10}H_7$
b	CH_3	C_6H_4OH (o-)
c	Cl	1-$C_{10}H_7$
d	Cl	C_6H_4OH (o-)



XII

	R
XII a	CH_3
b	Cl

acid was also prepared by the Jones oxidation of the carboxaldehyde IIIa and also via acid hydrolysis of the carbonitrile Va with sulphuric acid.

The reaction of the carboxaldehydes IIIa and IIIb with equimolar amount of hydrazine hydrate in boiling ethanol gave the corresponding hydrazones VIIa and VIIb, but on using half the equivalent amount of the hydrazine hydrate, the carboxyaldehyde bis-hydrazones VIIIa and VIIIb were obtained.

The IR spectra of VIIa,b exhibited bands at 3335, 3290 and 3150 (NH_2) and 1640 cm^{-1} (pyrone CO). Compounds VIIIa,b showed no IR bands due to NH_2 but displayed a band at 1640-1630 cm^{-1} due to pyrone CO. The PMR spectrum of VIIa exhibited signals at δ 8.25 (2H, *s*, NH_2, exchangeable with D_2O), 7.7 (1H, *s*, CH = N), 7.47 (3H, *s*, Ar-*H*), 6.6 (1H, *s*, H) and 2.36 (3H, *s*, CH_3).

The hydrazone VIIa when allowed to react with anisaldehyde and *o*-chlorobenzaldehyde in boiling ethanol gave the mixed hydrazones IXa and IXb respectively. Their IR spectra were devoid of a band due to NH function but exhibited a band at 1640-1630 cm^{-1} for pyrone CO.

4-Oxo-4*H*-1-benzopyrans in their reaction with phenylhydrazine behave like α,β-unsaturated ketones and the nucleophile attacks at C-2 with the opening of the pyrone ring[6]. But in the present study the carboxaldehydes IIIa and IIIb reacted easily with phenylhydrazine in boiling ethanol to form the carboxaldehyde phenylhydrazones Xa and Xb, respectively without the opening of the pyrone ring. The IR spectra of these compounds were devoid of a band due to CHO function but displayed bands at 1645 (pyrone CO) and 3350 cm^{-1} (NH).

With primary aromatic amines, 4-oxo-4*H*-1-benzopyrans undergo ring opening reaction[7]; however 4-oxo-4*H*-1-benzopyran-2-carboxaldehydes (IIIa and IIIb) reacted with primary aromatic amines ($R_1 - NH_2$) to give the corresponding schiff bases (XIa-d; Table 1). The IR spectra of XI showed bands at 1640 (pyrone CO) and 1610 cm^{-1} (C = N).

The carboxaldehydes IIIa and IIIb also reacted with ethylenediamine with the opening of the pyrone ring giving 3-(5'-methyl chloro-2'-hydroxymethylene)-5,6-dihydropyrazines (XIIa,b). Their IR spectra showed bands at 3260 (NH), 2900 (bonded OH) and 1630 cm^{-1} (α,β-unsaturated ketones).

According to Nohara[8], condensation of 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde with malonic acid gives 3-(4-oxo-4*H*-1-benzopyran-3-yl)acrylic acid. Accordingly the 2-carboxaldehydes IIIa and IIIb underwent condensation with malonic acid in pyridine at 115 to give the 2-acrylic acid derivatives (XIIIa and XIIIb) which on refluxing with abs. ethanol in the presence of conc. sulphuric acid gave the corresponding ethyl esters (XIIIc and XIIId; Table 2). The IR

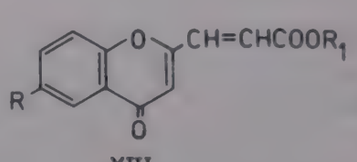
Table 1—Characterization Data of α-(4-Oxo-4*H*-1-benzopyran--2-yl)-N-(*p*-dimethylaminophenyl)nitrones (IIb-d) 4-Oxo-4*H*-1-benzopyran-2-carboxaldehydes (IIIa-d) and N-(4-Oxo-4*H*-1-benzopyran-2-ylidine)amines (XIa-d)

Compd	m.p. °C	Crystallized from	Yield (%)	Mol. formula	Found (%) (Calc.)				
					C	H	Br	Cl	N
IIb	217(d)	*n*-Butanol	76	$C_{18}H_{15}ClN_2O_3$	63.1	4.5	—	10.4	—
					(63.1	4.5	—	10.4	—)
IIc	221(d)	*n*-Butanol	73	$C_{18}H_{15}BrN_2O_3$	56.0	3.8	20.8	—	7.2
					(55.8	3.9	20.7	—	7.2)
IId	227(d)	Pyridine	69	$C_{22}H_{18}N_2O_3$	73.9	5.0	—	—	7.8
					(73.7	5.0	—	—	7.8)
IIIa	149	Pet. ether (100-120°)	68	$C_{11}H_8O_3$	70.0	4.9	—	—	—
					(70.2	4.3	—	—	—
IIIb	179	Pet. ether (100-120°)	72	$C_{10}H_5ClO_3$	57.6	2.6	—	17.0	—
					(57.5	2.4	—	17.0	—)
IIIc	206	Xylene	72	$C_{10}H_5BrO_3$	47.5	2.1	32.0	—	—
					(47.4	1.9	31.6	—	—)
IIId	210	Xylene	65	$C_{14}H_8O_3$	74.8	3.8	—	—	—
					(75.0	3.6	—	—	—)
XIa	150-51	Ethanol	50	$C_{21}H_{15}NO_2$	80.6	5.0	—	—	4.7
					(80.5	4.8	—	—	4.4)
XIb	230-32	Dioxane	59	$C_{20}H_{12}ClNO_2$	71.9	3.4	—	10.6	4.3
					(72.0	3.6	—	10.6	4.2)
XIc	215-17	Benzene	50	$C_{17}H_{13}NO_3$	73.7	4.7	—	—	5.2
					(73.3	4.6	—	—	5.0)
XId	220-22	Xylene	53	$C_{16}H_{10}ClNO_3$	64.3	3.2	—	11.7	4.5
					(64.1	3.3	—	11.8	4.7)

spectra of XIIIa,b showed bands at 3000-3500 (carboxylic OH), 1710 (carboxylic CO) and 1640 cm^{-1} (pyrone CO); and those of XIIIc,d at 1720 (ester CO) and 1645 cm^{-1} (pyrone CO). The PMR spectrum of XIIIa exhibited signals at δ 7.76 (1H, *s*, H-5), 7.6 (2H, *s*, H-7 and H-8), 7.26 (1H, *s*, H-3), 6.86-6.66 (2H, each *s*, CH = CH), and 2.3 (3H, *s*, CH_3), and that of XIIIc at δ 7.9 (1H, *s*, H-5), 7.73 (2H, *s*, H-7 and H-8), 7.4 (1H, *s*, H-3), 6.8, 6.52 (2H, each *s*, CH = CH), 4.66 (2H, *q*, CH_2), 2.38 (3H, *s*, CH_3) and 1.15 (3H, *t*, CH_2).

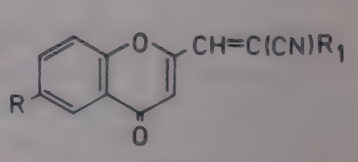
Condensation of IIIa and IIIb with malonodinitrile was facile in ethanol at room temperature giving XIV and XIVb, respectively (Table 2). Both the products showd $\nu C \equiv N$ at 2220 and pyrone νCO at 1665 cm^{-1}. The PMR spectrum of XIVa exhibited signals at δ 8.4 [1H, *s*, $CH = C(CN)_2$], 7.9 (1H, *s*, H-5), 7.6 (2H, *d*, J = 10 Hz, H-7 and H-8), 6.92 (1H, *s*, H_3) and 2.44 (3H, *s*, CH_3).

Condensation of IIIa and IIIb with ethyl cyanoacetate, cyanoacetic acid, and cyanoacetamide was conducted at 160° to give XIVc-h (Table 2). Nohara[9] found that 4-oxo-4*H*-1-benzopyran-3-carboxaldehydes undergo ring opening on treatment with cyanoacetamide to give pyridones, but in our case no ring opening occurred. Both XIVc and XIVd showed IR bands at 3000-2350 (carboxylic OH), 2330 ($C \equiv N$), 1720 (carboxylic CO) and 1630 (pyrone CO). XIVe and XIVf at 2220 ($C \equiv N$), 1725 (ester CO) and



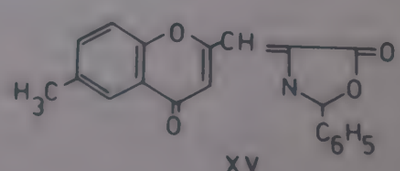
XIII

	R	R_1
XIIIa	CH_3	H
b	Cl	H
c	CH_3	C_2H_5
d	Cl	C_2H_5



XIV

	R	R_1
XIVa	CH_3	CN
b	Cl	CN
c	CH_3	COOH
d	Cl	COOH
e	CH_3	$COOC_2H_5$
f	Cl	$COOC_2H_5$
g	CH_3	$CONH_2$
h	Cl	$CONH_2$



XV

1650 (pyrone CO) and XIVg and XIVh at 3360, 3160 (NH_2), 2205 ($C \equiv N$), 1710 (amide CO) and 1640 cm^{-1} (pyrone CO). The PMR spectrum of XIVe exhibited signals at δ 8.8 (1H, *s*, $-CH = C(CN)-$), 7.9 (1H, *s*, H-5), 7.25-7.46 (2H, *m*, H-7 and H-8), 7.13 (1H, *s*, H-3), 4.43 (2H, *q*, CH_2), 2.46 (3H, *s*, CH_3) and 1.33 (3H, *t*, CH_3).

Table 2—Characterization Data of 3-(6-Methyl/chloro-4-oxo-4*H*-1-benzopyran-2-yl) acrylic Acids (XIIIa,b), Their Methyl Esters (XIIIc,d) and Other Derivatives (XIV)

Compd	m.p. °C	Crystallized from	Yield (%)	Mol. formula	Found (%) (Calc.)			
					C	H	Cl	N
XIIIa	279-81	AcOH	66	$C_{13}H_{10}O_4$	67.9	4.6	—	—
					(67.8	4.5	—	—)
XIIId	278-80	AcOH	55	$C_{12}H_7ClO_4$	56.9	2.6	13.9	—
					(57.5	2.8	14.1	—)
XIIIc	202-3	Ethanol	65	$C_{15}H_{14}O_4$	69.6	5.5	—	—
					(69.7	5.4	—	—)
XIIId	176-78	Ethanol	60	$C_{14}H_{11}ClO_4$	60.8	4.1	12.5	—
					(60.3	3.9	12.7	—)
XIVa	242-44	Ethanol	97	$C_{14}H_8N_2O_2$	70.9	4.0	—	11.9
					(71.1	3.4	—	11.8)
XIVb	269-71	Xylene	98	$C_{13}H_5ClNO_2$	61.1	1.8	13.9	11.1
					(60.8	2.0	13.8	10.9)
XIVc	240-42	Ethanol	52	$C_{14}H_9NO_4$	65.8	3.8	—	5.4
					(65.8	3.5	—	5.4)
XIVd	252-54	AcOH	48	$C_{13}H_6ClNO_4$	56.6	2.3	12.9	5.0
					(56.6	2.2	12.9	5.1)
XIVe	202-4	Ethanol	52	$C_{16}H_{13}NO_4$	67.6	4.6	—	4.7
					(67.8	4.6	—	4.9)
XIVf	195-97	Ethanol	62	$C_{15}H_{10}ClNO_4$	59.1	3.5	11.6	4.8
					(59.3	3.2	11.7	4.6)
XIVg	251-53	Dioxane	65	$C_{14}H_{10}N_2O_3$	66.4	3.8	—	11.2
					(66.1	3.9	—	11.0)
XIVh	244-46	Ethanol	58	$C_{13}H_7ClN_2O_3$	56.6	2.8	12.6	10.1
					(56.8	2.6	12.9	10.2)

It is known that condensation of aromatic aldehydes with hippuric acid gives oxazolones[10]. In the present study, condensation of IIIa with hippuric acid in boiling acetic anhydride in the presence of sodium acetate gave the oxazolone XV, the IR spectrum of which displayed bands at 1800 (azlactone CO), 1650 (pyrone CO) and 1620 cm^{-1} (C ≡ N).

Experimental Procedure

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 137 spectrophotometer, and PMR spectra in DMSO or (DMSO + D_2O) on a Varian EM-360 instrument.

α-(4-Oxo-4H-1-benzopyran-2-yl)-N-(p-dimethylamino-phenyl)nitrones (IIa-d; Table 1).

Nitrone IIa was prepared earlier by us[11]; IIb-d were prepared in a similar manner (see below).

To a solution of Ib-d (0.002 mol) and *p*-nitrosodimethylaniline (0.006 mol) in the least amount of ethanol, was added an ethanolic solution of sodium ethoxide (0.002 mol). The mixture was directly scratched with a glass rod and the red crystals that separated were filtered off and recrystallized from a proper solvent to give the nitrones IIb-d, respectively.

4-Oxo-4H-1-benzopyran-2-carboxaldehydes (IIIa-d; Table 1)

A mixture of IIa-d (1 g) and 10 *N* sulphuric acid (15 ml) was shaken at room temperature for 15 min, and water (50 ml) added to it. The solid that deposited was filtered, washed with water and crystallized from an appropriate solvent to give III.

6-Methyl and 6-chloro-4-oxo-4H-1-benzopyran-2-carboxaldehyde oximes (IVa and IVb)

A mixture of IIIa or IIIb (0.0015 mol) in pyridine (5 ml) and hydroxylamine hydrochloride (0.003 mol) in water (3 ml), was warmed for 5 min, cooled and acidified with dil. acetic acid. The solid obtained was collected and recrystallized from *n*-butanol to give IVa or IVb in 75% yield.

Alternatively the reaction was conducted in ethanol (10 ml) or in ethanolic hydrochloric acid (10 ml ethanol + 1 ml conc. HCl) for 5 min at the boiling point of the mixture to give the oxime IVa or IVb. IVa: m.p. 260 (Found: C, 64.8; H, 4.6; N, 6.7. $C_{11}H_9NO_3$ requires C, 65.0; H, 4.5; N, 6.8%). IVb: m.p. 265 (Found: C, 53.7; H, 2.9; Cl, 15.5; N, 6.0. $C_{10}H_6ClNO_3$ requires C, 53.7; H, 2.7; Cl, 15.8; N, 6.2%).

4-Oxo-4H-1-benzopyran-2-carbonitriles (Va and Vb)

A mixture of IVa or IVb (0.5 g) and acetic anhydride

(7 ml) was refluxed for 3½ hr, cooled and diluted with cold water. The resultant solid was filtered and recrystallized from ethanol to give Va or Vb in 55% yield. These compounds were found to be identical with authentic samples prepared according to the procedure of Ellis and Shaw[4].

6-Methyl-4-oxo-4H-1-benzopyran-2-carboxylic acid (VI)

It was prepared via two methods and was found to be identical with anauthentic sample prepared according to the method of Zagorevskii *et al.*[5]

(a) *By chromic acid oxidation of IIIa*—To a solution of IIIa (0.3 g) in acetone (5 ml),Jones reagent (2 ml) was added dropwise with stirring, and the reaction mixture filtered off. The solid product was treated with aq. sodium carbonate, filtered and the filtrate acidified with dil. hydrochloric acid to give VI.

(b) *By acid hydrolysis of Va*—Va (0.2 g) was refluxed for 3 hr with sulphuric acid (4 ml, 80%), the reaction mixture cooled, diluted with water and the solid formed filtered off to give VI.

6-Methyl- and 6-chloro-4-oxo-4H-1-benzopyran-2-carboxaldehyde hydrazones (VIIa and VIIb)

A solution of IIIa or IIIb (0.0015 mol) in ethanol (5 ml) was added to a solution of hydrazine hydrate (0.0015 mol) in ethanol (2 ml) and the mixture refluxed for 15 min, cooled and the solid obtained recrystallized from ethanol to give VIIa or VIIb; VIIa: m.p. 227-29°, yield 50% (Found: C, 65.1; H, 5.2; N, 13.7. $C_{11}H_{10}N_2O_2$ requires C, 65.4; H, 4.9; N, 13.9%); VIIb: m.p. 219-20°, yield 45% (Found: C, 53.8; H, 3.2; Cl, 16.0; N, 12.4. $C_{10}H_7ClN_2O_2$ requires C, 53.9; H, 3.1; Cl, 15.8; N, 12.6%).

6-Methyl- and 6-chloro-4-oxo-4H-1-benzopyran-2-carboxaldehyde bis-hydrazones (VIIIa and VIIIb)

Hydrazine hydrate (0.75 mmol) in ethanol (2 ml) was added to a solution of IIIa or IIIb (1.5 mmol) in ethanol (10 ml), and the reaction mixture refluxed for 15 min. The solid formed was filtered and recrystallized from acetic acid to give VIIIa or VIIIb in 70-75% yield; VIIIa: m.p. 264-66° (Found: C, 71.0; H, 4.4; N, 7.9. $C_{22}H_{16}N_2O_4$ requires C, 70.1; H, 4.3; N, 7.5%); VIIIb: m.p. 282-84° (Found: C, 58.1; H, 2.6; Cl, 16.7; N, 7.1. $C_{20}H_{10}Cl_2N_2O_4$ requires C, 58.1; H, 2.4; Cl, 17.2; N, 6.8%).

1-(6-Methyl/chloro-4-oxo-4H-1-benzopyran-2-ylidene-2-arylidene)hydrazines (IXa and IXb)

A mixture of VIIa (0.0015 mol) and the aromatic aldehyde (0.002 mol) in ethanol (10 ml) was refluxed for 1½ hr and left to cool. The solid formed was filtered and crystallized from acetic acid to give IXa or IXb: IXa: m.p. 265-66°, yield 66% (Found: C, 71.3; H, 4.9; N, 8.7. $C_{19}H_{16}N_2O_3$ requires C, 71.2; H, 5.0; N, 8.7%); IXb: m.p. 269-70°,yield 98% (Found: C, 66.4; H, 4.2; Cl, 11.0; N, 8.7. $C_{18}H_{13}ClN_2O_2$ requires C, 66.6; H, 4.0; Cl, 10.9; N, 8.6%).

6-Methyl- and 6-chloro-4-oxo-4H-1-benzopyran-2-carboxaldehyde phenylhydrazones (Xa and Xb)

To a solution of IIIa or IIIb (0.0015 mol) in ethanol (10 ml), phenylhydrazine (0.0015 mol) was added, the mixture refluxed for 15 min and cooled. The solid formed was filtered and recrystallized from an appropriate solvent to give Xa or Xb; Xa: crystallized from anisole, m.p. 253-55°, yield 48% (Found: C, 73.2; H, 5.3; N, 9.9. $C_{17}H_{14}N_2O_2$ requires C, 73.3; H, 5.0; N, 10.1%); Xb: crystallized from acetic acid, m.p. 257-59°, yield 52% (Found: C, 64.2; H, 3.7; Cl, 11.7; N, 9.2. $C_{16}H_{11}ClN_2O_2$ requires C, 64.0; H, 3.7; Cl, 11.9; N, 9.4%).

N-(4-Oxo-4H-1-benzopyran-2-ylidene)amines (XIa-d; Table 1).

A mixture of IIIa or IIIb (0.0015 mol) and the appropriate aromatic amine (α-naphthylamine or *o*-hydroxyaniline; 0.0015 mol) in ethanol (10 ml) was refluxed for 15 min and left to cool. The solid formed was filtered and recrystallized from an appropriate solvent to give XI.

3-(5'-Methyl/chloro-2'-hydroxybenzoylylidine)-5,6-dihydropyrazines (XIIa and XIIb)

A mixture of IIIa or IIIb (0.0015 mol) and ethylenediamine (0.0015 mol) in ethanol (5 ml) was left for 2 hr at room temperature. The solid formed was filtered and recrystallized from ethanol to give XIIa or XIIb in 65% yield; XIIa: m.p. 134-35° (*Found*: *C*, 67.8; *H*, 5.9; N, 11.9. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.1; N, 12.2%); XIIb: m.p. 175-76° (Found: C, 57.5; H, 4.5; Cl, 14.3; N, 11.1. $C_{12}H_{11}ClN_2O_2$ requires C, 57.4; H, 4.4; Cl, 14.5; N, 11.1%).

3-(6-Methyl/ chloro-4-oxo-4H-1-benzopyran-2-yl)acrylic acids (XIIIa and XIIIb)

A mixture of IIIa or IIIb (0.5 g) and malonic acid (0.5 g) in dry pyridine (3 ml) was heated at 110° for 1½ hr and left to cool. The solid formed was collected and recrystallized from a proper solvent to give XIIIa or XIIIb (Table 2).

Ethyl 3-(6-methyl/chloro-4-oxo-4H-1-benzopyran-2-yl) acrylates (XIIIc and XIIId)

To a solution of XIIIa or XIIIb (1 g) in abs. ethanol (10 ml), conc. sulphuric acid (2 drops) was added, and the mixture refluxed for 5 hr, evaporated and the solid left recrystallized from a proper solvent to give XIIIc or XIIId (Table 2).

1,1-Dicyano-2-(4-oxo-4H-1-benzopyran-2-yl)ethenes (XIVa and XIVb)

To a mixture of IIIa or IIIb (0.0015 mol) in ethanol (7 ml), malonodinitrile (0.0015 mol) in water (2 ml) was added. The solid deposited was filtered and recrystallized from a proper solvent to give XIVa or XIVb (Table 2).

2-Cyano-3-(6-methyl/chloro-4-oxo-4H-1-benzopyra 2-yl)acrylic acid derivatives (XIVc-h)

A mixture of IIIa or IIIb (0.0015ml) and the active methylene compound namely, cyanoacetic acid, ethyl cyanoacetate, and cyanoacetamide (0.0015 mol) was fused at 160° for 15 min, cooled and triturated with ethanol [pet. ether (60-80°) in the case of ethyl cyanoacetate]. The solid formed was collected and crystallized from a proper solvent to give XIV (Table 2).

4-(6-Methyl-4-oxo-4H-1-benzopyran-2-ylidene)-2-phenyl-5-oxazolone (XV)

To a mixture of hippuric acid (0.4 g) and anhyd. sodium acetate (0.2 g) in acetic anhydride (15 ml), IIIa (0.4 g) was added and the mixture refluxed for 5 min. The solid deposited after cooling was filtered and recrystallized from acetic anhydride to give XV in 53% yield, m.p. 248-50° (Found: C, 72.5; H, 4.0; N, 4.0. $C_{20}H_{13}NO_4$ requires C, 72.5; H, 4.0; N, 4.2%).

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Oxidation of Substituted 1-Hetera-4-cyclohexanols by N-Bromosuccinimide†

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The rates of NBS oxidation of some substituted 1-hetera-4-cyclohexanols have been measured at 50° in 80% acetic acid-20% water (v/v). The primary kinetic isotope effect is suggestive of the involvement of C – H or C – D bond of the hydroxy bearing carbon in the rate-determining step of the oxidation. The conformations of these compounds have been analysed on the basis of kinetic data and the rates of NBS oxidation for 4-piperidinols, 4-oxanols and 4-thianol-1,1-dioxides are found to differ considerably.

Despite considerable amount of information in the literature[1] on the versatility of NBS as an oxidising agent in the oxidation of alcohols and other organic substrates, a search of literature reveals work to have been carried out on the kinetics and mechanism of oxidation of only aliphatic[2], alicyclic[3-7], bicyclic[6] and steroidal[8,9] secondary alcohols. The present investigation was initiated in an effort to attain a better understanding of the mechanism and conformational effects on the NBS oxidation, rates of variously substituted six-membered heterocyclic secondary alcohols.

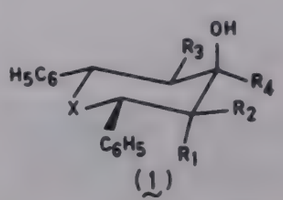
Materials and Methods

Compounds **1a-c**, **2a-c**[10], **1d-i**[11], **2d-i**[11], **1j-l**[12], **2j-l**[12], **3a**[11], **4a**[11], **3b**[12], **4b**[12], **5a**[10] and **5b-d**[12] were prepared as reported in literature. The deuterated piperidinols **1m-p** and **2m-p** were prepared by reducing 4-piperidones **6a-d** with lithium aluminium deuteride.

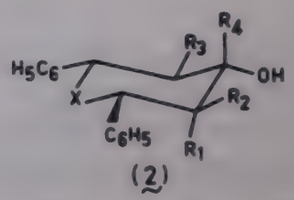
Acetic acid (Analar, B D H) was refluxed over CrO_3 and used as solvent. Other chemicals used were of Analar grade.

Lithium aluminium deuteride reduction of 4-piperidones: General procedure

To a stirred suspension of $LiAlD_4$ (0.02 mol) in dry ether (25 ml) was added dropwise a solution of 4-piperidone (0.02 mol) in dry ether (175 ml), and the mixture stirred at gentle reflux under nitrogen atmosphere for 24 hr. The excess of deuteride was decomposed by careful addition of ice-cold water. The ether layer was separated and the precipitated hydroxides were washed with ether (4 × 15 ml). The ethereal washings and the extracts were combined and dried ($MgSO_4$). Removal of ether in a rotary evaporator gave a mixture of axial and equatorial alcohols in 90% yield. The epimeric alcohols were separated by column chromatography following the procedure reported in literature[11] and recrystallized from pet. ether (b.p. 60-80°). Their yields and m.ps are recorded in Table 1.

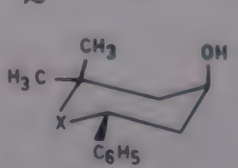


(1)



(2)

	X	R_1	R_2	R_3	R_4
a	O	H	CH_3	H	H
b	O	H	C_2H_5	H	H
c	O	H	CH_3	CH_3	H
d	NCH_3	H	H	H	H
e	NCH_3	H	CH_3	H	H
f	NCH_3	H	C_2H_5	H	H
g	NCH_3	H	i-C_3H_7	H	H
h	NCH_3	H	CH_3	CH_3	H
i	NCH_3	CH_3	CH_3	H	H
j	SO_2	H	H	H	H
k	SO_2	H	CH_3	H	H
l	SO_2	H	C_2H_5	H	H
m	NCH_3	H	H	H	D
n	NCH_3	H	CH_3	H	D
o	NCH_3	H	C_2H_5	H	D
p	NCH_3	H	i-C_3H_7	H	D



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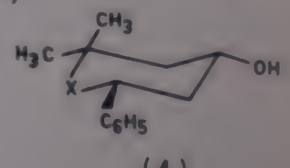
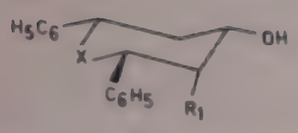


(4)

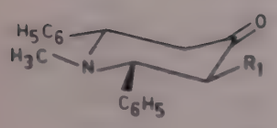
	X
a	NCH_3
b	SO_2

†This forms a part of M Jambulingam's thesis to be submitted.



(5)

	X	R_1
a	O	H
b	SO_2	H
c	SO_2	CH_3
d	SO_2	C_2H_5



(6)

	R_1
a	H
b	CH_3
c	C_2H_5
d	i-C_3H_7

Table 1—Composition of the Products from $LiAlD_4$ Reduction of 4-Piperidones

Piperidone used	Total crude product (%)	Yield (%) Axial	m.p. °C	Equatorial	m.p. °C
6a	97	10 (**1m**)	171-72	72 (**2m**)	163-64
6b	94	20 (**1n**)	71-72	56 (**2n**)	72-74
6c	96	26 (**1o**)[a]	139-40	52 (**2o**)[b]	74-75
6d	96	30 (**1p**)	105-6	40 (**2p**)	112-13

[a]MS: *m/z* 296.2000 (M^+) (Calc. 296.1999).
[b]MS: *m/z* 296.2005 (M^+) (Calc. 296.1999).

Kinetic measurements

Pseudo-first-order condition was maintained for all the kinetic runs by keeping the substrate and acid concentrations always in excess over that of NBS. Ionic strengths of the reaction mixtures were kept constant by the addition of sodium perchlorate. The reaction was carried out in darkened flasks to avoid photocatalysis. All experiments were conducted in a dark room wherein a yellow incandescent lamp was used. Solutions of alcohol and NBS containing mercuric acetate were kept at 50° for 1 hr. After mixing the reactant solutions, the final volume was made up to 30 ml. Portions (2 ml) of the reaction mixture were withdrawn periodically and quenched with potassium iodide solution (10 ml, 5%) containing 0.5 *M* sodium bicarbonate. The literated iodine was titrated against standard sodium thiosulphate (0.001 *N*) using starch (0.5 ml, 1%) as indicator. The reactions were followed for at least 70% utilisation of the oxidant and the results were found to be reproducible within ±2% error.

The reactions were carried out at 40°, 45°, 50° and 55°. A plot of $\log(k_2/T)$ versus $1/T$ gave a straight line. The enthalpy of activation ($\Delta H\ddagger$) and the entropy of activation ($\Delta S\ddagger$) were calculated from the slope and intercept respectively of the above plot, the slope being $-\Delta H\ddagger/2.303\,R$ and intercept being $\log(k/H)+\Delta S\ddagger/2.303\,R$ according to Eq. (1).

$$\log(k_2/T)=\log(k/h)+\Delta S\ddagger/2.303\,R-(1/T)\,\Delta H\ddagger/2.303\,R \quad \ldots (1)$$

Product analysis

A mixture of **2b** (1.5 g, 0.005 mol), NBS (1.1 g, 0.006 mol) and mercuric acetate (1.2 g, 0.004 mol) in 80% acetic acid - 20% water (v/v) (100 ml) was heated in a darkened round bottom flask fitted with a water condenser on a boiling water-bath for 4 hr. The reaction mixture was left at room temperature for 24 hr and poured on to crushed ice, filtered off, washed and dried. Crystallization of the residue from ethanol gave *r*-2, *cis*-6-diphenyl-*trans*-3-ethyl-4-oxanone (1.32 g, 88%), m.p. 104-5° (lit.[13], 104-5°). Similarly, the oxidation of **1f** and **1l** yielded exclusively the corresponding ketones.

Results and Discussion

The rates of oxidation of substituted 1-hetera-4-cyclohexanols (**1a-p**, **2a-p**, **3a**, **3b**, **4a**, **4b** and **5a-d**) by NBS were measured in 80% acetic acid - 20% water (v/v) at 50° following the disappearance of the oxidant by iodimetry and the results are given in Table 2. The second-order rate constants were calculated by dividing the pseudo-first-order rate constants (k_{obs}) with the respective alcohol concentrations. In most of our experiments to study the conformational effects on reaction rate, the ratio of [substrate] to [NBS] was kept at 10:1 such that the bromination of the product

Table 2—Second-order Rate Constants for the NBS Oxidation of Various Heterocyclic Secondary Alcohols

{Solvent: 80% acetic acid-20% water (v/v); $[HClO_4]=0.3\,M$; $[Hg(OAc)_2]=3.09\times10^{-3}\,M$; $I=0.5\,M$; temperature: 50°}

Compd	$10^2\times k_2$ (litre mol^{-1} s^{-1})	Compd	$10^2\times k_2$ (litre mol^{-1} s^{-1})
1a	20.28	**2a**	10.46
1b	31.44	**2b**	6.25
1c	6.71	**2c**	3.94
1d	16.45	**2d**	9.71
1e	32.06	**2e**	24.57
1f	40.78	**2f**	21.37
1g	64.19	**2g**	9.26
1h	8.05	**2h**	7.41
1j	41.78	**2i**	5.29
1k	60.20	**2j**	20.49
1l	104.15	**2k**	18.64
3a	12.67	**2l**	4.56
3b	35.40	**4a**	11.02
		4b	32.94
		5a	19.78
		5b	32.99
		5c	53.98
		5d	76.43

became kinetically insignificant. Since the ketonic products were present in too low a concentration under kinetic conditions, we were not able to isolate them quantitatively. The oxidation of a heterocyclic alcohol by NBS was carried out using excess of alcohol and the product analysis showed that alcohol was smoothly and quantitatively oxidised to the corresponding ketone in accordance with the observation of earlier workers[1]. For studying the effect of heteroatom on a curious dependence of rate on initial concentration as reported by Venkatasubramaniam and co-workers[7], the reaction rates were measured at varying concentration of the oxidant, and we found that heteroatoms did not have any effect on the oxidation mechanisms as reported. The dependence of rate on initial concentrations of succinimide, mercuric acetate, mercuric chloride and perchloric acid was also studied, and the results of these studies showed that the oxidation of heterocyclic alcohols followed the same path as reported earlier[7]. Further to complement the reported mechanism[7], the oxidation rates of the alcohols **1a**, **1d**, **1e**, **1j-l**, **2d** and **2e** with NBS were measured under identical conditions at different temperatures and the activation parameters (Table 3) evaluated. The positive entropy of activation ($\Delta S\ddagger$) is in good accord with the mechanism of the oxidation and serves as an evidence for the decomposition of the hypobromite ester in the rate-determining step[7].

The mechanism is also compatible with the observed isotope effect (Table 4). The large CH (CD) isotope effect ($k_H/k_D = 5.5$-7.5) provides further evidence for the mechanism involving decomposition of ester or hypobromite intermediate in the rate determining step.

Structure and reactivity

The substituted 1-hetera-4-cyclohexanols have been shown to exist in the anchored chair conformation with the alkyl and phenyl groups in the most stable equatorial position as no facile ring flipping or inversion, which leads to unfavourable conformations with increased steric interactions involving axial groups, is anticipated[10-15]. The difference in the oxidation rates of 1-hetera-4-cyclohexanols is strikingly similar to numerous observations for the oxidation of epimeric alicyclic alcohols by chromic acid[16-18]. The second-order rate constants (Table 2) for NBS oxidation of substituted heterocyclic alcohols indicate that the axial 1-hetera-4-cyclohexanols (**1a-g**) are oxidised at a faster rate than the equatorial epimers (**2a-l**) and also reveal that axial and equatorial epimers behave differently when there is an alkyl group vicinal to the $-OH$ function Eliel *et al.*[16] have analysed the results of chromic acid oxidation of substituted epimeric alcohols on the basis of non-bonded steric interactions and conformational effects and showed that the axial alcohols are oxidised at a faster rate than the corresponding equatorial isomers. In the present investigation we found that 1-hetera-4-cyclohexanols with equatorial OH are usually less susceptible to the NBS oxidation than the corresponding axial epimers, because in the former case the C–H bond is less accessible in the axial orientation, the rate-determining step being the rupture of this linkage and the strain in the ground state is relieved in the transition state[19].

In the alcohols **1a-g** with $-OH$ function in the axial orientation, an interesting observation in the oxidation rates is the effect of alkyl group adjacent to the reaction centre. The increased strain in the ring due the vicinal alkyl substituent as a result of non-bonded steric interactions is relieved during oxidation thereby enhancing the reaction rate. Therefore, 3-alkylheterocyclic alcohols reacted at a faster rate than the corresponding 2,6-diphenyl-4-heterocyclic alcohols. A comparison of the rate constants for the NBS oxidation of **1d-g** (Table 2) indicates that 3-alkyl substituent enhances the rate of oxidation: larger the size of the substituent, greater the oxidation rate which falls in the order **1g** > **1f** > **1e** > **1d** and parallels the order arrived at for increase in steric compression

Table 3—Activation Parameters for the Oxidation of 4-Heterocyclohexanols by NBS

{[NBS] = 8.10×10^{-4} *M*; [Substrate] = 10.70×10^{-3} *M*; [$HClO_4$] = 0.3 *M*; solvent: 80% HOAc-20% H_2O; [Hg $(OAc)_2$] = 3.09×10^{-3} *M*; *I* = 0.5 *M*}

Compd	$\Delta H\ddagger$ kJ mol^{-1})	$\Delta S\ddagger$ (J mol^{-1} K^{-1})
1a	−72.8	+71.8
1d	−83.7	+45.7
1e	−80.4	+48.6
1j	−90.4	+27.5
1k	−86.7	+45.6
1l	−82.7	+47.4
2d	−99.7	+ 5.0
2e	−90.4	+27.5

Table 4—Kinetic Isotope Effect in the NBS Oxidation of Alcohols

{Solvent: 80% acetic acid-20% water (v/v); temperature: 50°; [$HClO_4$] = 0.3 *M*; [$Hg(OAc)_2$] = 3.09×10^{-3} *M*; I = 0.5 *M*}

Compd	$10^2 \times k_2$ (litre mol^{-1} s^{-1})	$\frac{k_H}{k_D}$	Compd	$10^2 \times k_2$ (litre mol^{-1} s^{-1})	$\frac{k_H}{k_D}$
1d	16.45	7.48	**1p**	12.16	5.28
1m	2.20		**2e**	24.57	6.83
1e	32.06		**2n**	3.60	
1n	5.11	6.27	**2f**	21.37	
1f	40.78		**2o**	3.40	6.29
1o	6.04	6.75	**2g**	9.26	
1g	64.19		**2p**	1.57	5.90

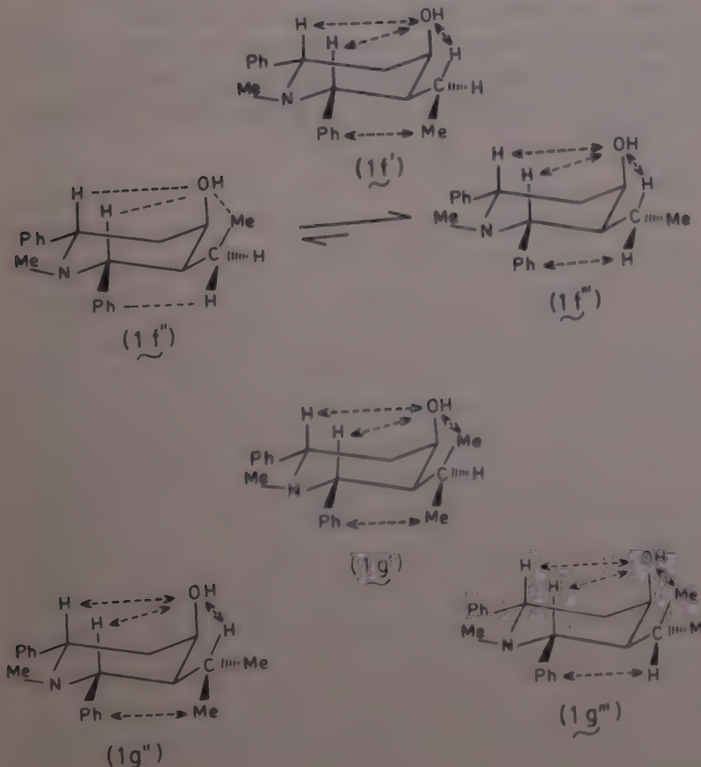
around the carbinol function as indicated by Courtauld model. The higher oxidation rates for *trans*-2, *trans*-6-diphenyl-*cis*-3-ethyl (**1f**) and *cis*-3-isopropyl-*cis*-N-methylpiperidin-*r*-4-ol (**1g**) when compared with 2,6-diphenyl-4-piperidinol (**1d**) could as well be explained based on the preferred conformation of alkyl group with respect to C_3-alkyl bond. The increased ease of oxidation of **1f** suggests that out of three conformers proposed, conformer **1f‴**, keeping the methyl group by rotation away from phenyl ring with three H – OH interactions, will exist mainly in the equilibrium mixture of **1f′** and **1f‴**.

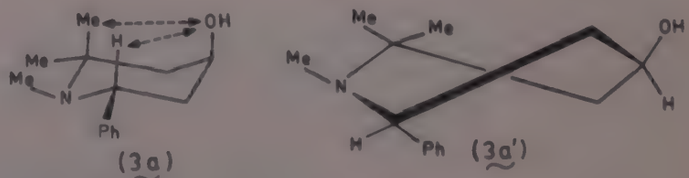
Likewise, the preferred configuration of 3-isopropyl group in *trans*-2, *trans*-6-diphenyl-*cis*-3-isopropyl-*cis*-N-methylpiperidin-*r*-4-ol (**1g**) reasonably anchors the conformation of the ring as **1g‴** and the higher rate constant is attributable to the presence of CH_3 – OH interactions in all the reacting species existing as **1g‴**. A similar trend is also found in oxygen and sulphur analogues.

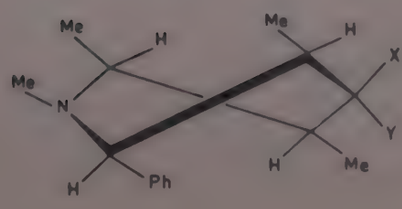
In general, in the all-equatorial series, the decelerating factor is observed, and hence the lowering in reaction rate for the piperidinols and thianols is presumably steric in origin, as the initial formation of the hypobromite may be rendered more difficult due to the equatorial alkyl group at position-3. Unfortunately, no such straight-forward interpretation can be given for the equatorial series and in fact, despite a considerable literature search we have not been able to come up with a complete explanation for the data in the equatorial series.

In *cis*-2, *trans*-2-dimethyl-*trans*-6-phenyl-N-methylpiperidin-*r*-4-ol (**3a**), the axially placed 2-methyl group will develop non-bonded 1,3-steric interactions with the axial –OH group and therefore should increase its oxidation rate. However, it undergoes oxidation considerably at a lower rate than the 2,6-diphenyl-4-piperidinol (**1d**), and infact its rate constant is more or less equal to that of the corresponding epimer **4a**. Hence, from the comparable rate constants of **3a** and **4a**, it is reasonable to assume that the axial 2-methyl group will exert little steric or polar effect on the reactivity of axial –OH group as the methyl group distorts the regular chair conformation. The probability of such distortion is greater in the case of the isomer **3a** as it possesses in the regular chair conformation one CH_3 ..... OH, one H ..... OH and one CH_3 ..... H interactions, amounting to the total repulsive interaction of about 15.49 kJ mol^{-1}. Conceivably the system may exist in twist conformation (**3a′**) or as deformed chair with equatorial like OH function, in which the non-bonded steric interactions have been alleviated to a large extent[13].

Success has been achieved particularly in arriving at the conformation of 2,6-diphenyl-3,5-dimethyl-4-piperidinols (**1h** and **2h**) and similarly constituted 4-oxanols (**1c** and **2c**), based on their NBS oxidation rates (Table 2). On comparison of the rate constants with that for 3-methyl-4-piperidinol (**1e**), one would be tempted to expect a greater increase in the oxidation rates for **1h** and **2h** due to increased gauche-interactions between CH_3 and OH groups. Surprisingly, they react even slower than the respective 3,5-unsubstituted 4-piperidinols (**1d** and **2d**) suggesting that the behaviour of **1h** and **2h** is not in accordance with a chair-conformation and the unexpectedly much lower rates of oxidation are therefore indicative of a decreased non-bonded gauche-interactions between OH and CH_3 groups, which is possible only in highly distorted chair or the twist conformation **1h′** and **2h′**. The assignment of such non-chair conformations to **1c**, **1h**, **2c**, **2h**, **3a** and **3b** also derives support from PMR and ^{13}C NMR chemical shifts[13,14].







	X	Y
(1h′)	OH	H
(2h′)	H	OH

The rate data given in Table 2 indicate that sulphone alcohols (**5b**, **5c** and **5d**) react at a faster rate than the corresponding 3-unsubstituted-*cis*-sulphone alcohols (**2j**). The X-ray studies[14] on **5c** and **5d** reveal that due to two axial groups (phenyl and alkyl), the ring is flattened at the carbinol carbon C-4, and the C_4-H_4 bond is forced away from the ring axis to "bent-downward" condition into a slightly more eclipsed position with C_3-alkyl bond which results in a smaller dihedral angle. In the light of this conformation coupled with the gauche-interaction and other internal molecular restrictions, the increased ease of oxidation of alcohols **5c** and **5d** by NBS can be explained. The reactivity order **5d** > **5c** > **5b** shows that the oxidation rate increases with the increase in size of the axial substituent at C-3.

The effect of a change in the heteroatom on the rate of oxidation may be seen from Table 2. Examination of the data in Table 1 reveals that the heteroatom effect is in the order $O < NCH_3 < SO_2$. The difference in reaction rate may be due to a combination of the polar effects of the heteroatom and the intrinsic conformation difference that exists due to different bond parameters of the heteroatom[13]. In the heterocyclic alcohols the degree of flattening of the ring depends upon the nature of the alcohol. The resulting subtle differences in the shape of the alcohols might in turn affect the reactivity of the heterocyclic alcohols.

Only for the substituted thian-*r*-4-ol-1,1-dioxides **1j-l**, **2j-l**, **3b**, **4b** and **5b-d**, the rates of oxidation by NBS were measured and we could not measure the reactions rates for the corresponding sulphide alcohols as the sulphide function is likely to be oxidised to sulphoxide or sulphone[20,21] function.

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Possible Anthelmintic Agents: Syntheses of Methyl 5(6)-Substituted-benzimidazole-2-carbamates†

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Syntheses of α-phenyl-[(2-methoxycarbonylamino)-5(6)-benzimidazolyl]propionitrile (**2**), α-phenyl-[(2-methoxycarbonylamino)-5(6)-benzimidazolyl]acrylonitrile (**3**), methyl 5(6)-hydroxymethylbenzimidazole-2-carbamate (**6**), β-[(2-methoxycarbonylamino)-5(6)-benzimidazolyl]acrylic acid (**9**), 2-methoxycarbonylaminobenzimidazole-5(6)-acetoxime (**13**) and 4-benzoyl-N-[5(6)-(2-methoxycarbonylamino)benzimidazolyl]pyrrolidin-2-one (**24**) are described. The structure of the latter (**24**) has been assigned on the basis of extensive ^{13}C NMR studies and ^{15}N signal of the model compound **19** obtained by reacting β-aroyl-γ-butyrolactone with *p*-anisidine. The compounds **2** and **3** at a single dose of 100 mg/kg exhibit 100% clearance of *A. ceylanicum* infection in hamsters.

In continuation of our studies[1,2] to understand the influence of substituents at position-5(6) of benzimidazole nucleus on the profile of anthelmintic activity of various benzimidazole-2-carbamates, a number of compounds (**2**, **3**, **6**, **9**, **13** and **24**) have now been synthesised and evaluated for their anthelmintic activity.

4-Acetyl- and 4-formyl-2-nitroacetanilides, identified as the starting materials for the synthesis of **2**, **3**, **6**, **9** and **13**, could be elaborated to the desired methyl benzimidazole-2-carbamate derivatives by straight forward reactions. For example, 4-formyl-2-nitroacetanilide (**25**) in the presence of a base reacted with benzyl cyanide to yield **1**. Catalytic hydrogenation of this compound followed by ring closure with a mixture of methyl chloroformate (MCF) and S-methylisothiouronium sulphate (SMIS) yielded **2** and **3** which were separated by column chromatography. Sodium borohydride reduction of **25** gave **4** which on hydrolysis funished **5**. Catalytic hydrogenation followed by ring closure of this compound with MCF and SMIS yielded **6**. Base-catalysed condensation of **25** with malonic acid furnished **7** which on deacetylation yielded **8**. The latter after careful hydrogenation and ring closure with MCF and SMIS yielded **9**. Compound **13** was obtained by oximation of **12**, which in turn was prepared by the method reported earlier[3] (Scheme 1).

Synthesis of **24** required a model study since substituted butyrolactones after ring opening with primary aromatic amines, in principle, can undergo recyclization to give compounds structurally related to either **21** or **18**. As a model study β-(*p*-toluoyl)-γ-butyrolactone (**16**), prepared from **14** by the method reported earlier[4], was reacted with *p*-anisidine. The structural assignment of the reaction product was primarily based on the ^{13}C NMR data (Scheme 2). Since the chemical shift of methylene carbon attached to the heteroatom in **16** and **22** (Scheme 2) is significantly different, the appearance of one of the methylene carbons at δ 50.58 supported the assigned structure **18**. Similarly compound **19** was prepared from **17**. The final support for the assigned structure was obtained from the ^{15}N signal at δ 33.689. Additional support for the assigned structure was obtained from the ^{13}C NMR spectrum of **20**, which was prepared by the catalytic hydrogenation of **18**.

On the basis of the analogy of the reaction of **16** and **17** with *p*-anisidine, the reaction product of **17** with 2-nitro-*p*-phenylenediamine was assigned the structure **23**. Careful catalytic hydrogenation of **23** followed by ring closure with MCF and SMIS yielded **24**.

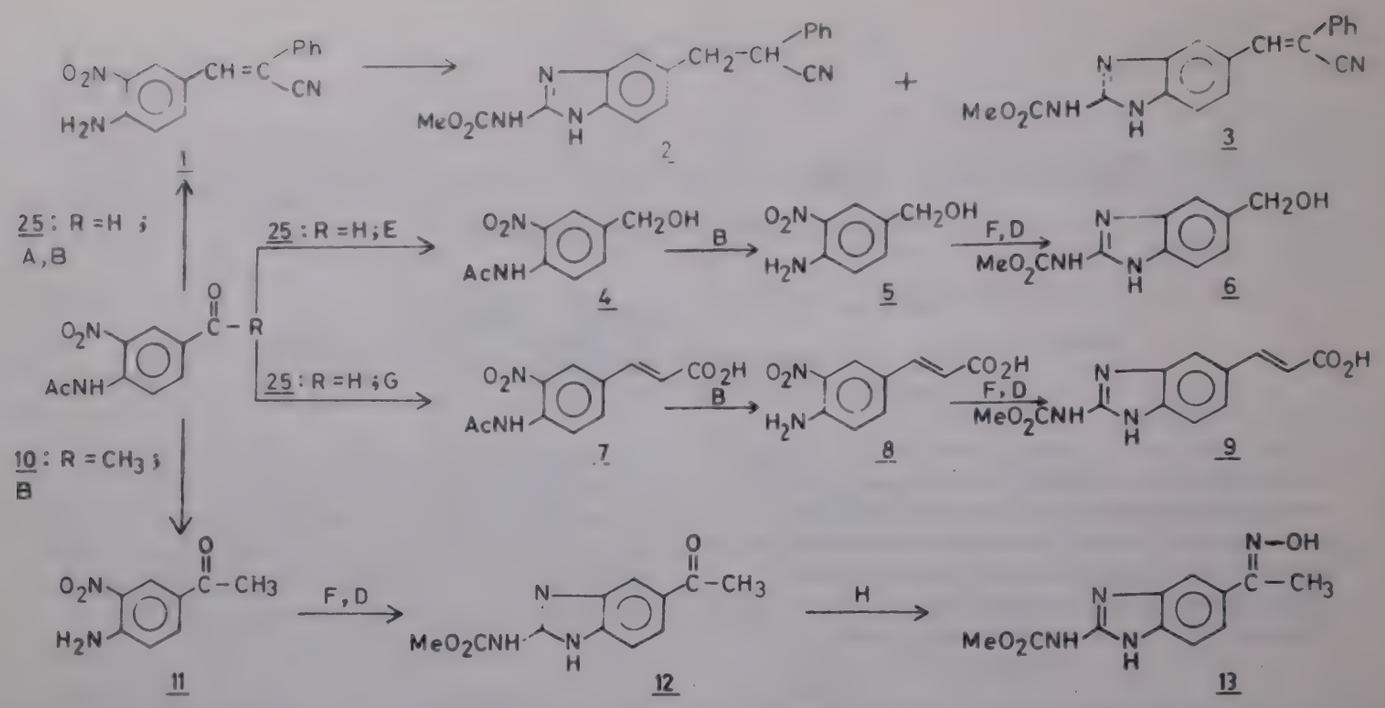
Biological activity

Almost all the compounds were evaluated for their anthelmintic activity against *H. nana* infection in mice and *A. ceylanicum* in hamsters. Compounds **2** and **13** induced 100% worm clearance of *A. ceylanicum* infection hamsters at a single dose of 100 mg/kg. Rest of the compounds were found to be inactive against both the infections mentioned above.

Experimental Procedure

Melting points were determined in H_2SO_4 bath or on an electrically heated block and are uncorrected. IR spectra were recorded on a Perkin-Elmer 157 infracord (ν_{max} in cm^{-1}) and PMR spectra on R-32 or EM-360L spectrometer using TMS as internal reference (chemical shift in δ, ppm). ^{13}C NMR spectra were recorded on a CFT-20 spectrometer. ^{15}N NMR

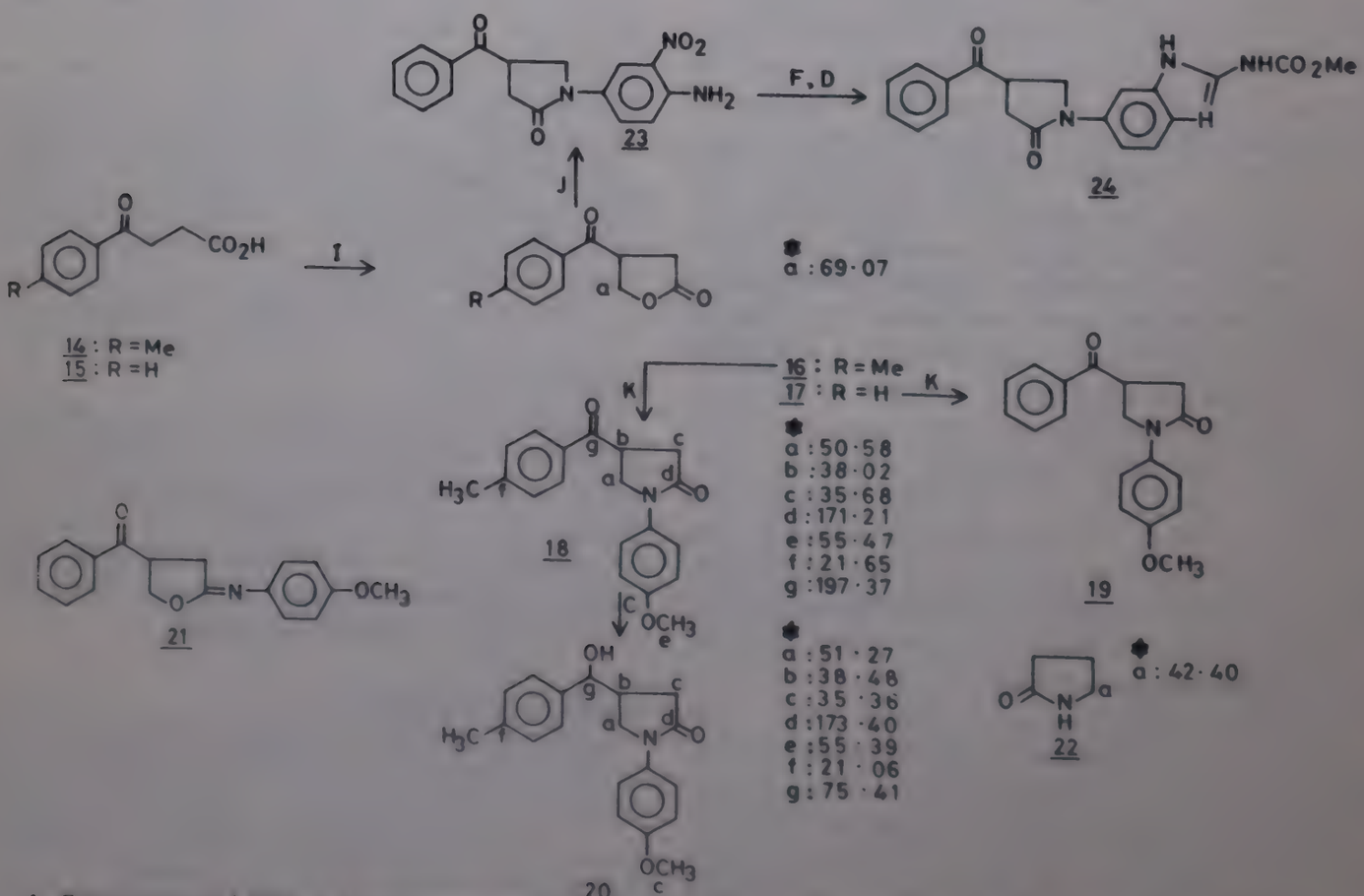
†CDRI Communication No. 3720.



A, $PhCH_2CN$; B, 10% aq. NaOH solution/MeOH; C, H_2, 10% Pd/c/MeOH; D, $HN=C(SMe)-NH_2$/$ClCO_2CH_3$;

E, $NaBH_4$/MeOH; F, H_2, Raney Ni/MeOH; G, Malonic acid, Pyridine/MeOH; H, $NH_2OH.HCl$, NaOAc/MeOH

SCHEME 1



I, Formaldehyde/HCl; J, 2-Nitro-p-phenylene diamine; K, p-anisidine; ●, ^{13}C-NMR data

SCHEME 2

spectrum was recorded on a Bruker WM-400 FT NMR spectrometer using formamide as internal reference. Mass spectra were recorded on a Jeol-JMS-D300 instrument.

α-Phenyl-(3-nitro-4-amino)cinnamonitrile (**1**)

To a solution of **25** (0.01 mole) and benzyl cyanide (0.01 mol) in methanol (10 ml) was added 10% aq. NaOH and the mixture refluxed for 1 hr. The precipitated solid was filtered, washed with water, dried and recrystallized from methanol, yield 63.4%, m.p. 239-40°, M^+ at *m/z* 265; IR(KBr): 2200 (CN) (Found: C, 67.7; H, 4.0; N, 15.9. $C_{15}H_{11}N_3O_2$ requires C, 67.9; H, 4.2; N, 15.8%); PMR(DMSO-d_6): 7.03-7.20 (*d*, 1H, CH, J=9 Hz), 7.37-8.17 (*m*, 9H, Ar-*H* and NH_2), 8.75-8.77 (*d*, 1H, Ar-*H* at position-2, J_m=2 Hz).

Catalytic hydrogenation of **1**: *Formation of α-phenyl-β-(3,4-diaminophenyl)propionitrile*

A solution of **1** (0.01 mol) in methanol (20 ml) was hydrogenated in the presence of 10% Pd/C (~50 mg) for 8 hr. The catalyst was filtered off and the solvent evaporated under reduced pressure. The residue so obtained was used in the next step without further purification and by assuming its yield as quantitative.

α-Phenyl-[(2-methoxycarbonylamino)-5(6)-benzimidazolyl]propionitrile (**2**) *and α-phenyl-[(2-methoxycarbonylamino)-5(6)-benzimidazolyl]-acrylonitrile* (**3**)

Aqueous NaOH solution (25%, 3 ml) was added under stirring to a precooled (10-15°) mixture of S-methylisothiouronium sulphate (0.01 mol) and methyl chloroformate (0.02 mol) in water (4 ml) and the *p*H of the reaction mixture maintained between 7.0 and 8.0. Glacial acetic acid was then added carefully for readjusting the *p*H to about 5 and to this mixture, was added the diamine (mentioned above, 0.01 mol) in methanol (15 ml). The reaction mixture was refluxed for 3 hr, cooled to room temperature and diluted with water (15 ml). The separated solid was filtered, washed with water, dried and chromatographed over silica gel using chloroform-ethyl acetate as eluent. Compound **2** was eluted first which was followed by compound **3**. Both of them were recrystallized from chloroform-hexane. Their characterization data are as follows: **2**: Yield 72.8%, m.p. 192°, M^+ at *m/z* 320; IR(KBr): 1720 (CO) and 2200 (CN) (Found: C, 67.2; H, 5.2; N, 17.4. $C_{18}H_{16}N_4O_2$ requires C, 67.5; H, 5.0; N, 17.5%); PMR($CDCl_3$ + DMSO-d_6): 3.10-3.19 (*d*, 2H, CH_2), 3.59-3.71 (*m*, 1H, CH), 3.78 (*s*, 3H, $NHCO_2CH_3$), 7.21 (*bs*, 8H, Ar-*H*).

3: Yield 5.0%, m.p. 189°, M^+ at *m/z* 318; IR(KBr): 1720 (CO), 2190 (CN) (Found: C, 67.9; H, 4.4; N, 17.2. $C_{18}H_{14}N_4O_2$ requires C, 67.9; H, 4.4; N, 17.6%); PMR($CDCl_3$ + DMSO-d_6): 3.76 (*s*, 3H, $NHCO_2CH_3$), 7.00-7.70 (*m*, 9H, Ar-*H* and =CH).

3-*Nitro*-4-*acetamidobenzyl alcohol* (**4**)

To a solution of **25** (0.01 mol) in methanol (10 ml) was added sodium borohydride (0.015 mol) at 5-10° under stirring. The reaction mixture was further stirred at room temperature for 30 min and after usual work-up it was extracted with ethyl acetate. Removal of the solvent and trituration of the residue with pet. ether furnished a solid which recrystallised from ethyl acetate-pet. ether to give **4**, yield 80%, m.p. 98°, M^+ at *m/z* 210; IR(KBr): 1700 (CO) (Found: C, 51.4; H, 4.5; N, 13.4. $C_9H_{10}N_2O_4$ requires C, 51.4; H, 4.7; N, 13.3%); PMR($CDCl_3$): 2.20 (*s*, 3H, CO_2CH_3), 4.60 (*s*, 2H, CH_2), 7.45-7.57 (*dd*, 1H, Ar-*H* at position-6, J_o=9 Hz, J_m=2 Hz), 8.10 (*s*, 1H, Ar-*H* at position-2), 8.50-8.60 (*d*, 1H, Ar-*H* at position-5, J_o=10 Hz).

4-*Amino*-3-*nitrobenzyl alcohol* (**5**)

To a solution of **4** (0.01 mol) in methanol (5 ml) was added 10% aq. NaOH solution (1 ml) and the resulting mixture stirred at room temperature for 30 min, water (5 ml) added to it and the reaction product extracted with ethyl acetate. Usual work-up yielded **5** which recrystallised from methanol, yield 81%, m.p. 90-91°, M^+ at *m/z* 168 (Found: C, 50.4; H, 4.5; N, 16.3. $C_7H_8N_2O_3$ requires C, 50.0; H, 4.8; N, 16.7%); PMR($CDCl_3$ + DMSO-d_6): 4.33 (*s*, 2H, CH_2), 6.50-7.23 (*m*, 5H, Ar-*H* and NH_2), 7.82 (*bs*, 1H, OH).

Catalytic hydrogenation of **5**: *Formation of* 3,4-*diaminobenzyl alcohol*

A solution of **5** (0.02 mol) in methanol (20 ml) was hydrogenated at 2.5 kg/cm^2 in the presence of Raney-Ni (~3 g) for 30 min. Catalyst was filtered off and solvent removed under reduced pressure. The residue containing the diamine was used without further purification in the next step.

Methyl 5(6)-*hydroxymethylbenzimidazole-2-carbamate* (**6**)

It was obtained from the above diamine following the method as described for the preparation of **2** and **3**. The reaction product (**6**) was recrystallised from DMF-H_2O, yield 67%, m.p. >300°; M^+ at *m/z* 221; IR(KBr): 1720 (CO), 3300 (NH); (Found: C, 54.3; H, 5.3; N, 19.2. $C_{10}H_{11}N_3O_3$ requires C, 54.3; H, 5.0; N, 19.0%); PMR(DMSO-d_6): 3.73 (*s*, 3H, $NHCO_2CH_3$), 4.50 (*s*, 2H, CH_2OH), 7.10-7.40 (*m*, 5H, Ar-*H* and 2 × NH).

4-*Acetamido*-3-*nitrocinnamic acid* (**7**)

To a mixture of **25** (0.01 mol) and malonic acid (0.01 mol) in ethanol (5 ml) was added pyridine (0.1 ml) and the reaction mixture refluxed for 2 hr. The separated

solid was filtered, washed with hot ethanol (5 ml), dried and recrystallised from DMF-H_2O to give **7**, yield 88%, m.p. 254-55°; M^+ at *m/z* 250; IR(KBr): 1620, 1690 (CO) (Found: C, 52.6; H, 3.8; N, 11.5. $C_{11}H_{10}N_2O_5$ requires C, 52.8; H, 4.0; N, 11.2%); PMR(DMSO-d_6): 2.08 (*s*, 3H, CO_2CH_3), 6.50-6.68 (*d*, 1H, =CH, *J*=16 Hz), 7.40-8.20 (*m*, 5H, Ar-*H*, =CH and NH).

4-Amino-3-nitrocinnamic acid (**8**)

Deacetylation of **7** to give **8** was carried out by the method as described for the preparation of **5**. It was recrystallised from DMF-H_2O, yield 90%, m.p. 206-7°; M^+ at *m/z* 208 IR(KBr): 1690(CO), 3350(NH) (Found: C, 52.2; H, 3.5; N, 13.1. $C_9H_8N_2O_4$ requires C, 51.9; H, 3.8; N, 13.5%); PMR(DMSO-d_6): 6.10-6.40 (*d*, 1H, =CH, *J*=16 Hz), 6.90-7.08 (*d*, 1H, $=CH-CO_2H$, *J* =12 Hz), 7.30-8.00 (*m*, 5H, Ar-*H* and NH_2).

Catalytic hydrogenation of **8**: *Formation of 3,4-diaminocinnamic acid*

The experimental procedure was essentially the same as described for the reduction of **5** and the resulting diamine was used in the next step without further purification.

β-[(2-Methoxycarbonylamino)-5(6)-benzimidazolyl]acrylic acid (**9**)

It was prepared from the above diamine by the method as described for **6** and was recrystallized from DMF-H_2O, yield 63%, m.p. >300°, M^+ at *m/z* 261; IR(KBr): 1650 (CO_2H), 1720 (CO) (Found: C, 55.1; H, 4.3; N, 15.8. $C_{12}H_{11}N_3O_4$ requires C, 55.2; H, 4.2; N, 16.0%); PMR(DMSO-d_6): 3.73 (*s*, 3H, CO_2CH_3), 6.24-6.41 (*d*, 1H, =CH, *J*=16 Hz), 7.10-7.78 (*m*, 4H, =CH and Ar-*H*).

2-Methoxycarbonylaminobenzimidazole-5(6)-acetoxime (**13**)

A mixture of hydroxylamine hydrochloride (0.15 mol) and sodium acetate (0.15 mol) in water (2 ml) was added to a solution of **12** (0.1 mol) in methanol (6 ml). The mixture was refluxed for 5 hr, cooled and diluted with water (10 ml). The solid so obtained was filtered, washed with water and recrystallised from DMF-H_2O to give **13**, yield 80%, m.p. 281-82°; M^+ at *m/z* 248; IR(KBr): 1640 (C=N), 1720 (CO), 3300 (NH) (Found: C, 53.1; H, 5.3; N, 22.2. $C_{11}H_{12}N_4O_3$ requires C, 53.2; H, 4.8; N, 22.6%); PMR(DMSO-d_6): 2.22 (*s*, 3H, CH_3), 3.80 (*s*, 3H, CO_2CH_3), 7.40-7.70 (*m*, 3H, Ar-*H*).

1-(4-Amino-3-nitrophenyl)-4-benzoylpyrrolidin-2-one (**23**)

To a mixture of **17** (0.1 mol) and 2-nitro-*p*-phenylenediamine (0.1 mol) in ethanol (6 ml) was added triethylamine (0.2 mol) and refluxed for 8 hr, water added to it and extracted with ethyl acetate. After usual work-up it was treated with ether to obtain a solid which recrystallised from ethyl acetate-ether to give **23**, yield 41%, m.p. >300°; M^+ at *m/z* 325; IR(KBr): 1680 (CO), 3300 (NH) (Found: C, 62.5; H, 4.4; N, 12.9. $C_{17}H_{15}N_3O_4$ requires C, 62.8; H, 4.6; N, 12.9%); PMR($CDCl_3$ + DMSO-d_6): 2.82-2.91 (*d*, 2H, 3-CH_2), 4.00-4.09 (*d*, 2H, 5-CH_2), 4.20-4.42 (*m*, 1H, CH), 6.87-8.08 (*m*, 10H, Ar-*H* and NH_2).

Catalytic hydrogenation of **23**: *Formation of 1-(3,4-diaminophenyl)-4-benzoylpyrrolidin-2-one*

The experimental procedure was essentially the same as described for the reduction of **5** and the resulting diamine was used without further purification in the next step.

4-Benzoyl-N-[5(6)-(2-methoxycarbonylamino)-benzimidazolyl]pyrrolidin-2-one (**24**)

It was prepared from the above diamine by the method as described for **6** and recrystallised from ethanol, yield 44%, m.p. >300°; M^+ at *m/z* 378; IR(KBr): 1640, 1720 (CO) (Found: C, 63.5; H, 4.4; N, 14.5. $C_{20}H_{18}N_4O_4$ requires C, 63.4; H, 4.8; N, 14.8%); PMR(DMSO-d_6): 2.40-2.70 (*d*, 2H, 3-CH_2), 3.60-4.58 (*m*, 6H, CO_2CH_3, 5-CH_2 and −CH), 6.30-7.62 (*m*, 8H, Ar-*H*), 7.85-8.05 (*bs*, 1H, NH).

4-Benzoyl/p-toluoyl-1-(p-methoxyphenyl)-pyrrolidin-2-one (**18**/**19**)

To a stirred solution of the appropriate lactone (0.04 mol) in ethanol (60 ml) was added the finely powdered *p*-anisidine (0.04 mol) followed by triethylamine (0.04 mol). The reaction mixture was refluxed for 5 hr, solvent removed and the residue extracted with benzene. The organic layer was washed with water, dried over anhyd. sodium sulphate and concentrated under reduced pressure to get a crystalline solid which recrystallised from benzene to give **18** or **19**. Their characterization data are as follows:

18: Yield 54%, M^+ at *m/z* 309; IR(KBr): 1700 (CO); PMR($CDCl_3$): 2.40 (*s*, 3H, CH_3), 2.90 (*d*, 2H, 3-CH_2), 3.74 (*s*, 3H, OCH_3), 3.90-4.20 (*m*, 3H, 5-CH_2 and −CH), 6.80-7.90 (*m*, 8H, Ar-*H*).

19: Yield 65%, m.p. 130-31°, M^+ at *m/z* 295; IR(KBr): 1705 (CO); PMR($CDCl_3$): 2.79-2.85 (*t*, 2H, CH_2), 3.70 (*s*, 3H, OCH_3), 3.90-4.21 (*m*, 3H, 5-CH_2 and −CH), 6.75-6.82 (*m*, 2H, Ar-*H*), 7.30-7.60 (*m*, 5H, Ar-*H*), 7.81-8.00 (*m*, 2H, Ar-*H*).

4-(γ-Hydroxy-4′-methylbenzyl)-1-(4′-methoxyphenyl)pyrrolidin-2-one (**20**)

A solution of **18** (3.0 g) in methanol (35 ml) was hydrogenated in the presence of Pd C (10%, 0.3 g) at

1.5 kg/cm^2 for 2 hr. The catalyst was filtered and the filtrate concentrated under reduced pressure. The residue on trituration with CCl_4 furnished a crystalline solid which recrystallised from hot CCl_4 to give **20**, yield 90%; M^+ at *m/z* 311; PMR($CDCl_3$): 2.30 (*s*, 3H, CH_3), 2.54-2.72 (*m*, 2H, 3-CH_2), 3.40-3.80 (*m*, 6H, OCH_3, 5-CH_2 and −CH), 4.40-4.60 (*m*, 1H, CHOH), 6.70-7.45 (*m*, 8H, Ar-*H*).

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Studies on Pyrazolines: Synthesis, Pyrolysis & Reactivity of Some 3-Aroyl-4-aryl-Δ^2-pyrazolines

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Δ^2-Pyrazolines (IIb-i) have been obtained through cycloaddition of diazomethane to chalcones (Ib-i). The structure (II) has been firmly established on the basis of PMR and ^{13}C NMR data. Pyrolysis and chemical reactivity of II are described. These compounds exhibit mild local anaesthetic, CNS depressant and anticonvulsant activities.

In continuation of studies[1,2] on pyrazolines from our laboratory, we report in this paper, synthesis, structure, pyrolysis, chemical reactivity and pharmacological activity of 3-aroyl-4-aryl-Δ^2-pyrazolines (IIb-i).

The desired IIb-i were synthesized through cycloaddition of diazomethane to chalcones (Ib-i), which in turn were obtained by crossed aldol condensation of appropriately substituted benzaldehydes and acetophenones. Earlier reports[3-5] suggested two alternate structures (II) and (III) for these pyrazolines.

Recently, Sayed *et al.*[5] obtained Δ^2-pyrazolines (IIIh-l), through the above reaction, as mixtures of 4,5-syn- and 4,5-anti-isomers and consequently interpreted the PMR and mass spectral data on the basis of structure (III). However, a critical examination of PMR assignments points out that (i) the olefinic C_3-H appears at a considerably higher field (δ 4.45-4.70), which is unusual for the protons of this nature[6] and (ii) the ^3J(H-4, H-5); ^3J(H-3, H-4) and ^3J(H-4, H-5) in the case of both 4,5-syn- and 4,5-anti-isomers are reported to be equal, whereas some difference in the case of two isomers is expected. Therefore, a reexamination of PMR data of IIb-i was made. The multiplets in the regions δ 4.45-4.70, 3.90-4.10 and 3.60-3.70 could be attributed to the protons H_X, H_M and H_A ($J_{AX}=6$ Hz; $J_{MX}=10$-12 Hz) in structure (II). The PMR spectra were recorded both at 90 MHz and 270 MHz and there was no change in the spacings within the multiplets. Hence, there was no need to invoke 4,5-syn- and 4,5-anti-isomerism in these pure products. Spectra taken on samples after several crystallisations gave identical results. Spin experiments on H_A signal brought about changes in H_M and H_X signals, as expected for a 12-line AMX pattern.

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Further, 3-benzoyl-4-methyl-4-phenyl-Δ^2-pyrazoline (V), obtained by the addition of CH_2N_2 to dypnone (IVa) followed by isomerisation and devoid of hydrogen on C-4, exhibited in its PMR spectrum only two doublets ($J=10$ Hz) at δ 3.45 and 3.57 assignable to C-5 protons, thus, favouring structure (II) for the Δ^2-pyrazolines. In case of structure (III) two singlets for C_3-H and C_5-H would have appeared. Further ^{13}C NMR spectra of IIa, h, i exhibited triplets around δ 57.0 and doublets around 48.0 attributable to C-5 and C-4 carbons respectively in structure (II).

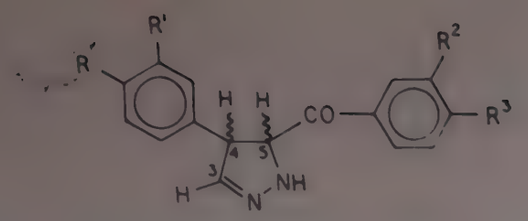
Δ^2-Pyrazolines (IId, e, i) exhibited N-H proton at δ 6.60, (exchangeable with D_2O) and coupled to H_M ($J=2$ Hz), confirmed by decoupling experiments. From the foregoing, it is clear that 3-aroyl-4-aryl-Δ^2-pyrazolines have structure (II). Such a structural assignment has also been favoured by Auwers *et al.*[3] and Kohler *et al.*[3] but without any spectral evidence. Mass spectral data are consistent with the structures deduced.

Pyrolysis

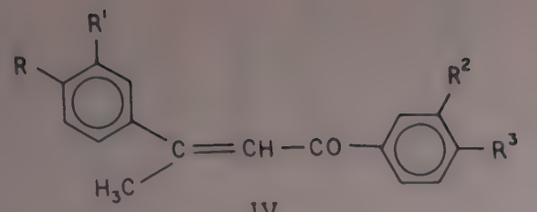
Pyrolysis of Δ^2-pyrazolines (IIb, c, h) at 190°C for 2 hr in the presence and absence of solvents gave, as expected[7] the corresponding β-methylchalcones (IVb-d) in 70-75% yield. Other pyrazolines (IId-g, i) did not yield any recognisable products under the same conditions. It may be noted with interest in this context that low temperature thermolysis, however, gave rearranged 3,5-diaryl-4-pyridazinones[2].

Chemical reactivity

Δ^2-Pyrazolines (IIa, h, i) on heating with formic, acetic, propionic and butyric acids under reflux, as reported[8] gave the corresponding N-acyl derivatives (VIa-j). But, valeric and other higher fatty acids, instead, produced the corresponding pyrazoles. Aromatic, haloacetic acids and anhydrides did not yield any isolable products.



III



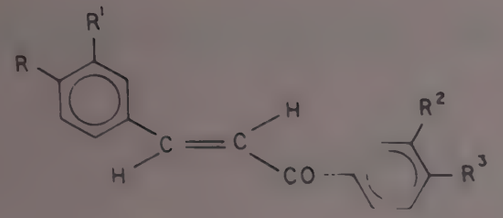
IV

a) $R = R' = R^2 = R^3 = H$

b) $R = R' = R^2 = H$; $R^3 = OCH_3$

c) $R = R^2 = R^3 = H$; $R' = OCH_3$

d) $R = OCH_3$; $R' = R^2 = R^3 = H$



I

a) $R = R' = R^2 = R^3 = H$

b) $R = R' = R^2 = H$. $R^3 = OCH_3$

c) $R = R^2 = R^3 = H$; $R' = OCH_3$

d) $R = R^2 = R^3 = H$. $R' = NO_2$

e) $R = R' = R^3 = H$. $R^2 = NO_2$

f) $R = NMe_2$, $R' = R^2 = H$. $R^3 = OCH_3$

g) $R = NMe_2$; $R' = R^2 = R^3 = H$

h) $R = OCH_3$; $R' = R^2 = R^3 = H$

i) $R = NO_2$. $R' = R^2 = R^3 = H$

j) $R = OCH$, $R' = R^2 = H$; $R^3 = OCH_3$

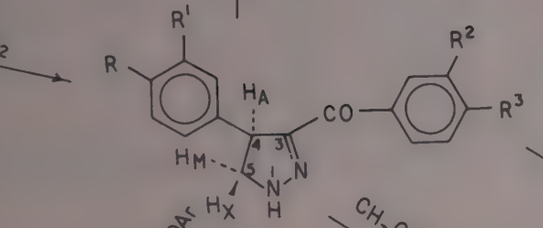
k) $R = NO_2$. $R' = R^2 = H$; $R^3 = OCH_3$

l) $RR' = -OCH_2O-$, $R^2 = R^3 = H$

m) $R = R' = R^2 = H$; $R^3 = NO_2$

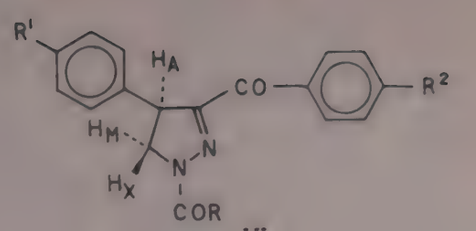
CH_2N_2

Δ



II

$R-COOH$



VI

a) $R = R' = R^2 = H$

b) $R = CH_3$; $R' = R^2 = H$

c) $R = CH_2CH_3$; $R' = R^2 = H$

d) $R = CH_2CH_2CH_3$; $R' = R^2 = H$

e) $R = R^2 = H$; $R' = OCH_3$

f) $R = CH_3$, $R' = OCH_3$, $R^2 = H$

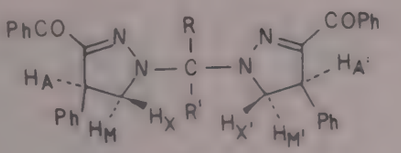
g) $R = CH_2CH_3$, $R' = OCH_3$, $R^2 = H$

h) $R = CH_2CH_2CH_3$; $R' = OCH_3$; $R^2 = H$

i) $R = R' = H$, $R^2 = NO_2$

j) $R = CH_3$; $R' = H$; $R^2 = NO_2$

$R-CO-R'$



VII

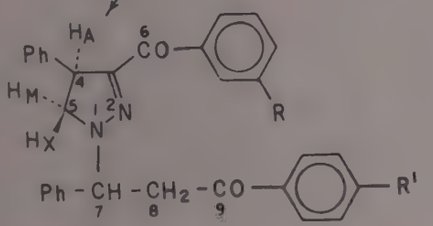
a) $R = R' = CH_3$

b) $R = CH_3$; $R' = CH_2CH_3$

c) $RR' = -(CH_2)_4-$

d) $RR' = -(CH_2)_5-$

$PhCH=CHCOAr$



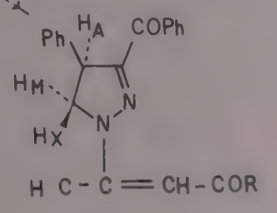
IX

a) $R = R' = H$

b) $R = H$; $R' = NO_2$

c) $R = NO_2$; $R' = H$

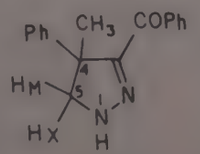
CH_3COCH_2COR



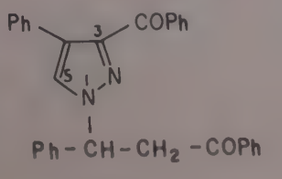
VIII

a) $R = CH_3$

b) $R = OCH_2CH_3$



V



X

Δ^2-Pyrazoline (IIa) reacted with simple ketones, such as acetone, ethyl-methyl ketone, cyclopentanone and cyclohexanone, when heated under reflux and gave N-analogues (VIIa-d) of ketals. Structures of these compounds have been supported by PMR and mass spectral data. Aldehyes, however, did not yield recognizable products. This is the first report on reactivity of Δ^2-pyrazolines with simple carbonyl compounds.

IIa reacted with excess acetylactone and acetoacetic ester under reflux and yielded enamine type compounds, VIIIa and VIIIb respectively. The products were characterised through spectral data.

Δ^2-Pyrazolines (IIa, e) on heating with α,β-unsaturated carbonyl compounds, such as chalcones (Ia, m) at 130° for 90 min gave the isomeric β-substituted dihydrochalcones (IXa-c). The isomers in each case could be separated by preparative TLC on silica gel. These isomers differed only in their melting points and had almost identical spectral data, precluding structural isomerism. These dihydrochalcones (IXa-c) possess two asymmetric centres, C-4 and C-6 and hence, these may be diastereoisomers. However, the reaction with 3(5)-benzoyl-4-phenylpyrazole and chalcone (Ia) resulted in the isolation of only one product, which was characterised as X.

Pharmacological activity

Δ^2-Pyrazolines (IIa-i) exhibited mild, local anaesthetic, CNS depressant and anticonvulsant activities. The Δ^2-pyrazolines or the N-acyl derivatives did not show any significant larvicidal, synergistic activity, JH and antifeedant activities. These did not act as stomach or contact poison.

Experimental Procedure

Melting points were determined on VEB Analytik Dresden (HMK 73/4329) instrument and are uncorrected. UV spectra were recorded in ethanol on a Beckmann DB-G spectrophotometer and IR spectra in KBr on a Perkin-Elmer 237 grating infrared spectrophotometer, PMR spectra in $CDCl_3$ or CCl_4 on a Perkin-Elmer R32 NMR spectrometer operating at 90 MHz or a Bruker WH 270 MHz instrument and ^{13}C NMR on a XL-100 NMR spectrometer operating at 25.2 MHz or on a Bruker WH 270 MHz instrument (FT mode) operating 67.89 MHz; chemical shifts are expressed and recorded in δ (ppm) from TMS internal reference. Mass spectra were recorded on a Varian MAT CH-7 instrument.

All the compounds reported in this paper gave satisfactory elemental analyses and spectral data are consistent with the structures. The chalcones (Ib-i, m) were prepared according to literature procedures. Aromatic aldehydes and substituted acetophenones and other chemicals used were obtained commercially and purified before use.

Cycloaddition of diazomethane to chalcone (I): General procedure for Δ^2-pyrazolines (IIa-i)

To a solution of I (1 g) in dry ether or chloroform at 0°C was added diazomethane (from 2 g of nitrosomethylurea) and kept at 0°. The progress of the reaction was monitored by TLC. After completion of reaction, the solvent was removed by passing dry air and the products were crystallised (the compounds thus prepared are listed in Table 1).

Pyrolysis of Δ^2-pyrazolines (IIb, c, h): Formation of β-methylchalcones (IVb-d)

The Δ^2-pyrazolines (II, 1 g) were heated at 190°C for 2 hr in a metal bath. The progress of the reaction was followed by loss in weight as well as on silica gel layers. After completion of reaction, the products were chromatographed over silica gel to obtain pure β-methylchalcones (IVb-d) which are listed in Table 1.

3-Benzoyl-4-methyl-4-phenyl-Δ^2-pyrazoline (V)

To a solution of dypnone (IVa, 1 g) in dry ether (25 ml) was added diazomethane (from 2 g of

Table 1—Physical Data of IIa-i, IVb-d, V, VIa-j, VIIa-d, VIIIa,b

Compd	Reaction time (hr)	Yield (%)	m.p. (°C)	Mol. formula
IIb	48	99	115-16	$C_{17}H_{16}O_2N_2$
IIc	48	98	161-62	$C_{17}H_{16}O_2N_2$
IId	1	95	102-3	$C_{16}H_{13}O_3N_3$
IIe	1	92	162-63	$C_{16}H_{13}O_3N_3$
IIf	200	94	132-33	$C_{19}H_{21}O_2N_3$
IIg	200	93	103-4	$C_{18}H_{19}ON_3$
IIIh	48	100	145-46	$C_{17}H_{16}O_2N_2$
IIi	1	94	134-35	$C_{16}H_{13}O_3N_3$
IVb	1	73	69-71	$C_{17}H_{16}O_2$
IVc	1	870	liquid	$C_{17}H_{16}O_2$
IVd	1	70	-do-	$C_{17}H_{16}O_2$
V	—	45	-do-	$C_{17}H_{16}ON_2$
VIa	2	90	126-28	$C_{17}H_{14}O_2N_2$
VIb	2	90	118-20	$C_{18}H_{16}O_2N_2$
VIc	2	95	145-46	$C_{19}H_{18}O_2N_2$
VId	2	95	108-10	$C_{20}H_{20}O_2N_2$
VIe	2	90	126-28	$C_{18}H_{16}O_3N_2$
VIf	2	95	129-30	$C_{19}H_{18}O_3N_2$
VIg	2	95	110-12	$C_{20}H_{20}O_3N_2$
VIh	2	98	131-32	$C_{21}H_{22}O_3N_2$
VIi	2	90	178-80	$C_{17}H_{13}O_4N_3$
VIj	2	95	110-12	$C_{18}H_{15}O_4N_3$
VIIa	2	80	186-88	$C_{35}H_{32}O_2N_4$
VIIb	4	65	154-56	$C_{36}H_{34}O_2N_4$
VIIc	8	50	148-50	$C_{37}H_{36}O_2N_4$
VIId	8	45	174-76	$C_{38}H_{38}O_2N_4$
VIIIa	6	50	140	$C_{21}H_{20}O_2N_2$
VIIIb	6	50	178-80	$C_{23}H_{22}O_2N_2$

nitrosomethylurea) in ether and kept at room temperature for 9 days. The solvent was removed and the residual mass on the chromatography over silica gel afforded 3-benzoyl-4-methyl-4-phenyl-Δ^1-pyrazoline, which crystallised from chloroform-methanol, m.p. 153-54°, yield 0.5 g. This Δ^1-pyrazoline was heated at 155-60° for 50 min to give a liquid, which on chromatography gave pure V as a yellow liquid.

Reaction of Δ^2-pyrazolines (II) with fatty acids

A mixture of Δ^2-pyrazoline (II, 0.10 g) and aliphatic acid (1 ml) was refluxed for 90 min. Progress of the reaction was monitored on silica gel layers. After completion of the reaction, the excess acid was removed *in vacuo*, the residue washed with aq. $NaHCO_3$ and the solid recrystallised from ethanol. The N-acyl-Δ^2-pyrazolines (VIa-j) were obtained in almost quantitative yields and are listed in Table 1.

Reaction of II with carbonyl compounds:
With ketones

Method (1): IIa (0.50 g) and ketone (5 ml) was heated under reflux on a steam-bath for 2-8 hr. The reaction mixture was left overnight in a refrigerator and the solid separated was filtered and crystallised.

Method (2): A mixture of II (0.50 g) and ketone (0.2 ml) in benzene (10 ml) was refluxed on a steam-bath for 2-8 hr and left overnight at room temperature to afford VIa-d, which crystallised from suitable solvents (not listed in Table 1).

With acetylacetone and acetoacetic ester

The procedure for simple ketones described above, was followed to obtain VIIIa and VIIIb.

Reaction of Δ^3-pyrazolines (II) with chalcones (I)

A mixture of IIa (0.25 g, 0.001 mol) and Ia (0.21 g, 0.001 mol) was heated on a metal-bath at 130-40° C, for 2 hr. The reaction mixture was separated on preparative silica gel layers to give diastereoisomers IXa(i) and IXa(ii) which were crystallised (Table 2).

Table 2—Physical Data of IXa(i)-IXc(ii) and X

Compd	Yield (%)	m.p. (°C)	Mol. formula
IXa(i)	33	81-82	$C_{31}H_{26}O_2N_2$
IXa(ii)	36	132-34	$C_{31}H_{26}O_2N_2$
IXb(i)	40	69-70	$C_{31}H_{25}O_4N_3$
IXb(ii)	30	62-64	$C_{31}H_{25}O_4N_3$
IXc(i)	22	164-66	$C_{31}H_{25}O_4N_3$
IXc(ii)	23	65-66	$C_{31}H_{25}O_4N_3$
X	24	151-52	$C_{31}H_{24}O_2N_2$

The same procedure was used for the reaction of 3(5)-benzoyl-4-phenyl-1*H*-pyrazole with Ia to give X.

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Synthesis & Biological Activity of Some 5-Substituted 1,2,5a,11b,11c-Hexahydro[1]benzopyrans[4,3-*d*]pyrazolo-[3,4-*b*]pyridine-1,6-diones & 5*H*-4a,10b-Dihydrobenzopyrans-[3,4-*c*]pyridine Derivatives

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3-Acetyl- and 3-carbethoxy-coumarins (**1a,b**) react with cyanoacetic acid hydrazide (**2**) in the presence of piperidine at room temperature to give the corresponding dihydrocoumarin derivatives (**3a,b**) which can be converted into the pyrazolopyridine (**4a**) and pyrazolopyridone (**4b**) derivatives respectively on boiling their ethanolic solutions in the presence of piperidine. The latter compounds (**4a,b**) can also be prepared by the reaction of **1a,b** with 3-amino-2-pyrazoline-5-one in the presence of piperidine. Under similar conditions coumarins **1a** and **1b** react with 1,1,3-tricyano-2-aminopropene (**5a**) and 3-carbethoxy-1,1-dicyanopropene (**5b**) to give the benzopyran[3,4-c]-pyridines (**7a,8a**) and benzopyran[3,4-c]pyridones (**7a,8b**), respectively. Some of the compounds have been screened for their antibacterial activity.

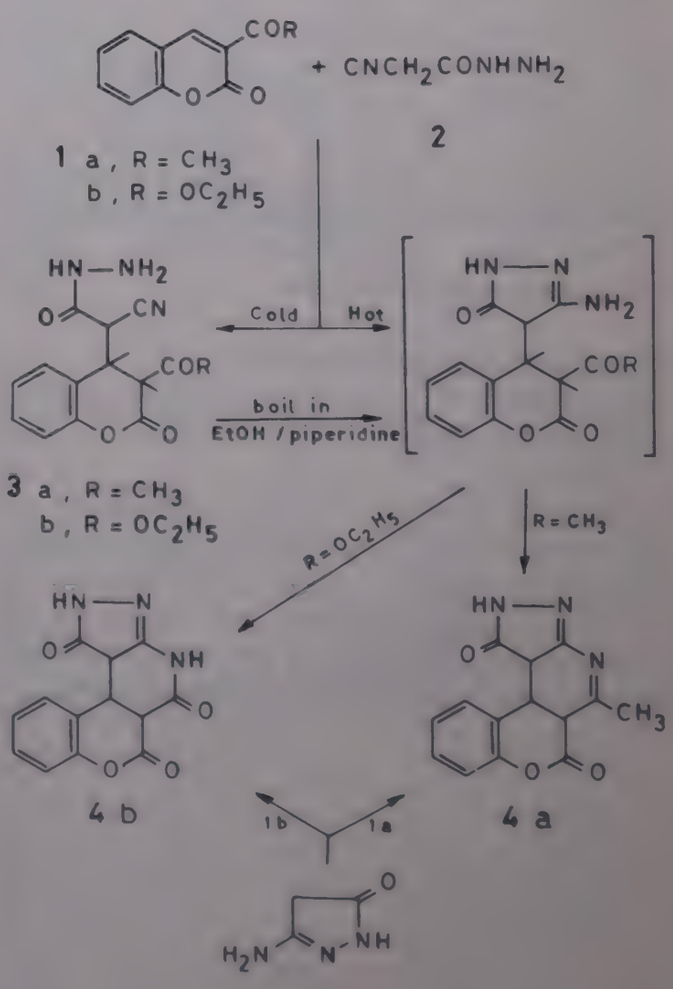
It has been observed that 3-substituted coumarins posses significant antibacterial[1], coronary dilatory[2] and hypothermal[3] activities. Therefore, it became of interest to synthesize new coumarinopyridine and coumarinopyridone derivatives of possible biological activities.

3-Acetyl- and 3-carbethoxy-coumarins (**1a,b**) were reacted with cyanoacetic acid hydrazide (**2**) in the presence of piperidine at room temperature to give the corresponding 3-substituted 3,4-dihydrocoumarin-4-cyanoacetic acid hydrazides (**3a,b**) (Scheme 1). This is in agreement with the findings of Sastry and Seshadri[4].

The structures of **3a,b** were established on the basis of their elemental analyses and spectral data. Their IR spectra exhibited absorption bands due to CN, NH, NH_2 and C=O functions. The PMR data supporting the structures **3a** and **3b** are given in Table 1.

Compounds **3a,b** could, however, be converted into the pyrazolopyridine (**4a**) and pyrazolopyridone (**4b**) derivatives respectively by boiling their ethanolic solutions in the presence of a catalytic amount of piperidine. The structure **4** was established by elemental analyses and spectral data. An unequivocal support for this structures was achieved by synthesis via the reaction of **1a,b** with 3-amino-2-pyrazolin-5-one in boiling ethanol in the presence of piperidine (Scheme 1).

Compounds **1a,b** also reacted with 2-amino-1,1,3-tricyanopropene (**5a**) under similar experimental conditions to afford the benzopyran[3,4-c]pyridine



Scheme 1

(**7a**) and benzopyran[3,4-c]pyridine (**7b**) derivatives, respectively. It is presumed that the above reaction proceeds via Michael addition of the active methylene group of **5a** to the activated double bond in **1** to afford

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Table 1 – Characterization Data of Various Compounds Prepared (3, 4, 7 and 8)

Compd	Cryst. from	Colour	Yield %	m.p. °C	Mol. formula	Analyses %		PMR (δ ppm)
						Found	Calc.	
3a	EtOH	Colourless	85	180	$C_{14}H_{13}N_3O_4$	C 58.7 H 4.4 N 14.8	58.5 4.5 14.6	3.2 (*s*,3H,CH_3), 4.6 (*s*,1H,CH), 4.8 (*m*,2H,benzopyran H-3 and H-4), 6.2 (*s*,2H, NH_2), 7.3-7.9 (*m*,4H,Ar – *H*), 9.9 (*s*,1H,NH).
3b	EtOH	Colourless	80	133	$C_{15}H_{15}N_3O_5$	C 56.6 H 4.6 N 13.4	56.7 4.7 13.2	1.16 (*t*,3H,CH_3), 4.1 (*q*,2H,CH_2), 4.6 (*s*,1H,CH), 4.8 (*m*,2H,benzopyran H-3 and H-4), 6.3 (*s*,2H,NH_2), 7.2-7.8 (*m*,4H,Ar – *H*), 9.4-9.8 (*s*,1H,NH).
4a	$CHCl_3$	Reddish	70	>280	$C_{14}H_{11}N_3O_3$	C 62.5 H 4.1 N 15.3	62.4 4.1 15.6	3.0 (*s*,3H,CH_3), 3.5 (*m*,3H,3CH), 7.4-7.8 *m*,4H,Ar – *H*), 9.9-10.1 (*s*,1H,NH).
4b	$CHCl_3$	Orange	60	280	$C_{13}H_9N_3O_4$	C 57.4 H 3.0 N 15.7	57.5 3.3 15.5	
7a	EtOH-$CHCl_3$	Reddish	65	>300	$C_{17}H_{10}N_4O_2$	C 67.8 H 3.4 N 18.7	67.5 3.3 18.5	
7b	$CHCl_3$	Yellow	55	280	$C_{16}H_8N_4O_3$	C 63.3 H 2.5 N 18.6	63.2 2.6 18.4	3.7 (*m*,1H,pyran H-4), 4.2 (*s*,1H,NH), 4.8 (*m*,1H,pyran H-3), 6.9-7.6 (*m*,4H,Ar – *H*).
8a	EtOH	Wine red	70	>280	$C_{19}H_{15}N_3O_4$	C 65.5 H 4.4 N 12.3	65.3 4.3 12.0	1.9 (*t*,3H,CH_3), 3.0 (*s*,3H,CH_3), 3.2 (*s*,1H,CH), 3.5 (*m*,2H,pyran H-4 and H-3), 4.3 (*q*,2H,CH_2), 6.6-7.6 (*m*,4H,Ar – *H*).
8b	EtOH	Greenish yellow	70	225	$C_{18}H_{13}N_3O_5$	C 61.6 H 3.5 N 11.7	61.5 3.7 12.0	

the acyclic Michael intermediate **6** which undergoes cyclization to give **7** (Scheme 2). The structure **7** was established by elemental analyses and spectral data. The IR spectra of **7a** and **7b** displayed absorption peaks due to CN, C=O and C=N functions. In addition to these bands, the IR spectrum of **7b** exhibited a band due to NH function. The PMR data of **7a** and **7b** (cf. Table 1) agreed well with their proposed structures.

The coumarins **1a,b** reacted with 2-amino-3-carbethoxy-1,1-dicyanopropene (**5b**) in the presence of piperidine to give the corresponding benzopyrano[3,4-c]pyridine (**8a**) and benzopyrano[3,4-c]pyridone (**8b**) derivatives, respectively. The proposed structures **8a** and **8b** were established by their IR and PMR spectral data (Table 1).

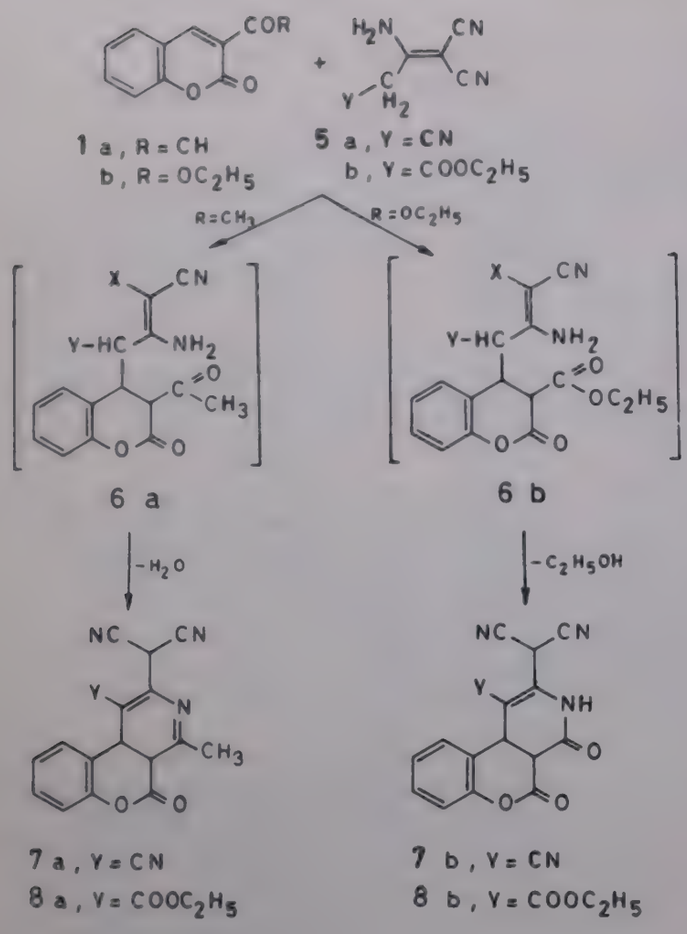
Antibacterial activity

Some of the benzopyranopyridine and benzopyranopyridone derivatives were tested for their antibacterial activity *in vitro* against the microorganisms *Staphylococcus aureus*, *Bacillus subtilis*, *E. coli* and *Pseudomonas aeruginosa* at 10 mg/ml concentration on the nutrient broth and nutrient agar media following the Kirby-Bauer filter paper disc method[6]. The results are given in Table 2. It is worth noting that compound **4a** is highly active against *S. aureus*.

Table 2 – *In vitro* Action of Benzopyranopyridine Derivatives on Various Strains of Bacteria

Compd	Inhibitory Effect on			
	E coli	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*
3a	–		+	+
3b	+ +		+	+
4a	–	+	+ +	+ + +
7a	+ +	–	–	+
8a	+	–	+	–
8b	+ +	–	+	+

0 centimeter = negative (–)
up to 1 centimeter = slightly active (+)
up to 2 centimeter = moderately active (+ +)
up to 3 centimeter = highly active (+ + +)



Scheme 2

Experimental Procedure

Melting points are uncorrected. IR (KBr) spectra were recorded on a Schmatzu 408 spectrophotometer, and PMR spectra in DMSO on a 60 MHz EM-360 instrument.

3-Substituted-3,4-dihydrocoumarin-4-cyanoacetic acid hydrazides (**3a**,**b**): *General procedure*

To a mixture of **1** (0.01 mol) and cyanoacetic acid hydrazide (0.01 mol) in ethanol (30 ml) was added 3 drops of piperidine and the reaction mixture stirred at room temperature. After 10-15 min a colourless precipitate appeared which was filtered and crystallized from ethanol to get **3** as colourless crystals (Table 1).

5-Methyl- and 5(4H)-oxo-1,2,5a,6,11b,11c-hexahydro-[1]-benzopyrans[4,3-d]-pyrazolo[3,4-b]pyridine-1,6-diones (**4a** *and* **4b**)

Method (*A*) – Compound **3a** or **3b** (0.01 mol) was refluxed in ethanol (20 ml) in the presence of piperidine (3 drops) for 1 hr and the reaction mixture cooled. The resultant solid was filtered and crystallized from ethanol to give **4a** or **4b** (Table 1).

Method (*B*) – A mixture of **1a** or **1b** (0.01 mol), 2-amino-2-pyrazolin-5-one (0.01 mol) and piperidine (3 drops) was refluxed in ethanol (30 ml) for 1 hr. The reaction mixture was left to cool and the resultant solid filtered and crystallized from a suitable solvent to get **4a** or **4b** (Table 1).

Benzopyran[3.4-c]pyridine derivatives (**7** *and* **8**): *General procedure*

A mixture of **1** (0.01 mol), the active methylene reagent (**5a** or **5b**; 0.01 mol) and piperidine (3 drops) was refluxed in ethanol (30 ml) for 1 hr and cooled. The precipitated solid was filtered and crystallized from a suitable solvent to get **7** or **8** (Table 1).

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Notes

Synthesis of 3-O-Methylanhydrotuberosin†

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The structure of the naturally occurring pterocarpene, 3-O-methylanhydrotuberosin as 3-methoxy-10,10-dimethyl-6*H*,10*H*-furo-[3,2-*c*; 4,5-*g*']bis[1]benzopyran (**5**) has been confirmed unequivocally by its synthesis.

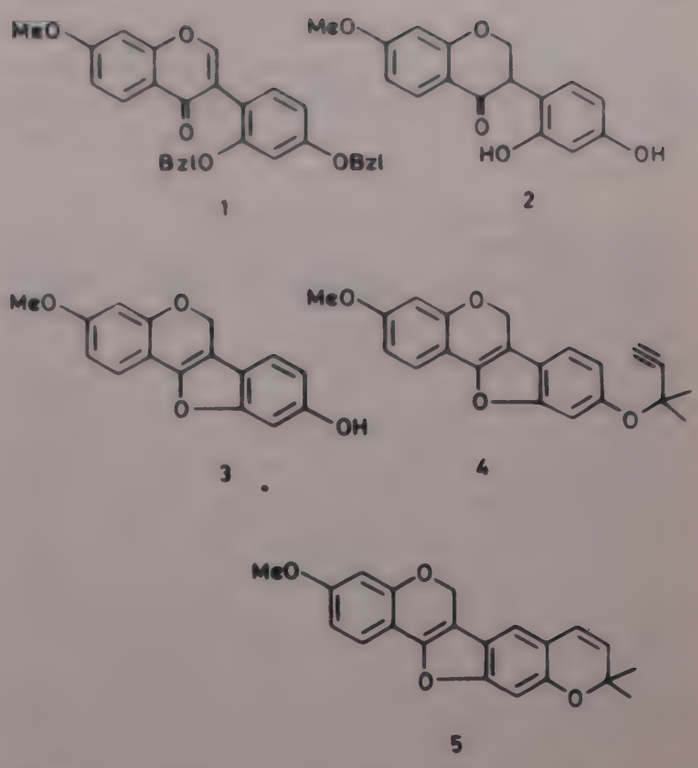
Recently[1,2] we have reported the isolation of several new pterocarponoids from the tubers of *Pueraria tuberosa*. The common structural feature of all these pterocarponoids is a linearly disposed 2,2-dimethylchromene ring, constituting the ring-D of the pterocarponoid skeleton. In this note, we present rigorous proof for the confirmation of the structure of 3-O-methylanhydrotuberosin[2] as 3-methoxy-10,10-dimethyl-6*H*,10*H*-furo[3,2-*c*; 4,5-*g*']bis[1]benzopyran (**5**), through its synthesis.

Catalytic hydrogenation (10% Pd/C) of the isoflavone (**1**) in acetone followed by purification through column chromatography and PLC over silica gel gave the requisite isoflavanone[3] (**2**). Acid-catalysed ring closure of **2** in methanol using HCl at 98° for 3 hr followed by purification of the product by column chromatography over silica gel afforded 3-methoxy-9-hydroxypterocarpene (**3**) in 31% yield. Condensation of **3** with 2-chloro-2-methylbut-3-yne in the presence of K_2CO_3 and KI resulted in the formation of the propargyl ether (**4**; 88% yield), which on Claisen rearrangement by heating with N,N-dimethylaniline at 210° afforded a mixture from which 3-O-methylanhydrotuberosin (**5**) isolated in 20% yield. This was spectroscopically and chromatographically indistinguishable from the natural product.

2',4'-Dihydroxy-7-methoxyisoflavanone (**2**) was prepared from the isoflavone (**1**) by the method described earlier[3].

3-*Methoxy*-9-*hydroxypterocarpene* (**3**)

A mixture of **2** (700 mg), methanol (100 ml) and HCl (3 ml) was heated under stirring at 98° for 3 hr, concentrated, diluted with water, extracted with chloroform, the organic extract washed with water and dried (Na_2SO_4). Removal of the solvent afforded an oily product which was passed through a small column of silica gel. Elution with hexane-chloroform (1 : 1) and crystallization furnished **3** (200 mg), m.p. 134°; UV (MeOH): 270-290 (br), 306, 320 and 335 nm; PMR ($CDCl_3$; TMS internal ref.): δ 3.70 (*s*, 3H, OCH_3), 5.43 (*s*, 2H, H-6), 6.35-6.70 and 6.90-7.20 (*m*, 5H, Ar-H) and 7.25 (*d*, 1H, $J = 9.0$ Hz, H-1); MS: *m/z* 268 (M^+), 267 (100%), 253, 224, 197 and 134.



1 2 3 4 5

3-*Methoxy*-9-(1,1-*dimethylpropargyl*)*oxypterocarpene* (**4**)

A mixture of **3** (55 g) and K_2CO_3 (100 mg) in acetone (15 ml) was stirred at room temperature for 30 min. To this solution, 2-chloro-2-methyl-but-3-yne (0.25 ml) and KI (100 mg) were added and the mixture refluxed for 12 hr. Additional amounts of K_2CO_3 (50 mg) and the chloro compound (0.25 ml) were then added and the mixture was boiled for another 24 hr. It was cooled, filtered, solvent evaporated, the residue dissolved in dichloromethane, washed with water and dried (Na_2SO_4). Removal of the solvent afforded **4** which was purified by passing through a small column of silica gel. Elution with hexane-chloroform (70 : 30) gave pure **4** (60 mg) as an oil (yield, 88%); UV (MeOH): 232 (sh), 276) (infl), 320, 324 and 352 (sh) nm; IR (neat): 3300 and 2200 (C≡CH) cm^{-1}; PMR ($CDCl_3$): δ 1.58 [*s*, 6H, $C(CH_3)_2$], 2.50 (*s*, 1H, C≡C−H), 3.70 (*s*, 3H, OCH_3), 5.48 (*s*, 2H, H-6), 6.40 to 7.30 (*m*, 5H, Ar-H) and 7.35 (*d*, 1H, $J = 8.5$ Hz, H-1); MS: *m/z* 334 (M^+), 319 and 267 (100%).

†CDRI Communication No. 3752.

3-O-Methylanhydrotuberosin (**5**)

The propargyl ether (**4**, 50 mg) was heated with N,N-dimethylaniline (1 ml) at 210° for 6 hr. Dilute HCl (10 ml) was then added to this solution and extracted with chloroform. The chloroform extract was washed successively with dil. HCl, water and dried (Na_2SO_4). Removal of the solvent afforded a complex mixture from which **5**, m.p. 163° (10 mg) (yield, 20%) was isolated by PLC over silica gel.

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Synthesis of 5,6-Dimethoxy-7,3′,4′-trihydroxyflavone

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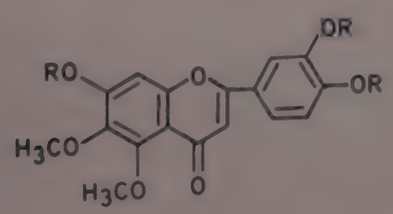
5,6-Dimethoxy-7,3′,4′-trihydroxyflavone (I), a new flavone isolated from the aerial parts of *Anisomeles ovata* has been synthesised starting from 4-benzyloxy-2-hydroxy-5,6-dimethoxy-acetophenone (IV). The m.p. and spectral data (UV, IR, PMR) of synthetic I tally with those reported for the natural compound.

Rao and Kumari[1] recently isolated a new flavone from the aerial parts of *Anisomeles ovata* and formulated it as 7,3′,4′-trihydroxy-5,6-dimethoxyflavone (I) on the basis of its spectral data. In this note we provide synthetic proof for structure I.

4-Benzyloxy-2-hydroxy-5,6-dimethoxyacetophenone (IV), obtained as an oil by methylation [$(CH_3)_2SO_4$-K_2CO_3-acetone-method] of 4-benzyloxy-2,5-dihydroxy-6-methoxyacetophenone, on condensation with 3,4-dibenzoyl chloride gave 2-(3,4-dibenzyloxy-benzoyloxy)-4-benzyloxy-5,6-dimethoxy-acetophenone (V). Baker-Venkataraman transformation of V resulted in 2-hydroxy-3′,4′,4-tribenzyloxy-5,6-dimethoxybenzoylmethane (VI) which on cyclisation afforded 7,3′,4′-tribenzyloxy-5,6-dimethoxyflavone (II). Catalytic debenzylation of II afforded 5,6-dimethoxy-7,3′,4′-trihydroxyflavone (I), the m.p. and spectral data (UV, IR, PMR) tallied with those of natural I. Pentamethyl ether (III) of synthetic I had m.p. identical to that reported[2].



I) R = H
II) R = $-CH_2C_6H_5$
III) R = CH_3

2-(3,4-Dibenzyloxy-benzoyloxy)-4-benzyloxy-5,6-dimethoxy-acetophenone (V)

A mixture of IV (1 g), 3,4-dibenzyloxy benzoyl chloride (2.5 g) and dry pyridine (5 ml) was heated on a steam-bath for 3 hr. Usual work-up afforded V as a brown semi-solid (800 mg). It did not respond to ferric chloride reaction. It was fully characterised by its IR and PMR data.

2-Hydroxy-3′,4′,4-tribenzyloxy-5,6-dimethoxy-benzoylmethane (VI)

The above ester V (700 mg) in anhydrous pyridine (4 ml) was treated with powdered KOH (1 g) and the mixture shaken vigorously for 2 hr with occasional warming. The cooled reaction mixture was treated with ice-HCl (1:1) and the precipitated yellow solid, filtered, washed with water, dried and crystallised from EtOAc-petrol to afford VI as yellow crystals (450 mg), m.p. 127-29°. It gave blue colour with alc. $FeCl_3$; IR (KBr): 1680, 1580, 1478, 1450, 1395, 1255 and 1015 cm^{-1}; PMR ($CDCl_3$): δ 3.72 and 3.95 (3H each, *s* each, 2× $-OCH_3$), 5.18 (6H, *m*, 3× $-OCH_2C_6H_5$), 6.30 (1H, *s*, H-3) and 7.13-7.51 (19H, *m*, 3× $-OCH_2C_6H_5$, H-2′, 5′ and 6′ and $-CO-CH=C-OH$), 12.94 (1H, *s*, $-COCH=C-OH$).

7,3′,4′-Tribenzyloxy-5,6-dimethoxyflavone (II)

The diketone (VI, 400 mg) was gently refluxed with gl. CH_3COOH (8 ml) and fused NaOAc (800 mg) in an oil-bath for 3 hr. The usual work-up afforded II which was purified by preparative TLC (EtOAc-petrol, 3:17) and crystallized (EtOAc-petrol) as brown needles (150 mg), m.p. 206-8°. It did not respond to alc. $FeCl_3$; IR(KBr): 1680, 1583, 1450, 1340, 1190, 1020 and 920 cm^{-1}; PMR ($CDCl_3$): δ 3.76 and 3.95 (3H each, *s* each, 2× $-OCH_3$), 5.15-5.18 (6H, *m*, 3× $-OCH_2C_6H_5$), 6.28 (2H, *s*, H-3 and H-8) and 7.11-7.52 (18H, *m*, 3× $-OCH_2C_6H_5$, H-2′, 5′, 6′).

5,6-Dimethoxy-7,3′,4′-trihydroxyflavone (I)

II (125 mg) in EtOAc (20 ml) was stirred under H_2 atmosphere in the presence of Pd/C (15 mg, 10%) for 5 hr. Usual work-up provided I which crystallised as yellow powder (MeOH) 40 mg, m.p. 296-97°. It gave a positive Mg/HCl test and a positive ferric reaction: IR(KBr): 2820, 1600, 1450, 1370, 1220, 1010 and 950 cm^{-1}; UV (MeOH): 252, 270, 342 nm; $+AlCl_3$: 275, 306, 390 nm; $+AlCl_3$/HCl: 260, 275, 356 nm; +NaOAc: 270, 385 nm; +NaOAc/H_3BO_3: 265, 365 nm; and +NaOMe: 265, 390 nm; PMR ($CDCl_3$): δ 3.81 and 3.90 (3H each, *s* each, 2× $-OCH_3$), 6.26 (1H, *s*, H-8), 6.38 (1H, *s*, H-3), 7.01 (1H, *d*, J = 8 Hz, H-5′), 7.18 (1H, *d*, J = 3 Hz, H-2′) and 7.47 (1H, *q*, J = 8, 3 Hz, H-6′); pentamethyl ether (III): m.p. 176-78° (EtOAc-petrol) (lit. m.p. 178-79°).

All compounds gave satisfactory C, H analysis.

S R (S R F) and S K G (Pool Officer) thank the CSIR, New Delhi and M G (P D F), the Centre of Advanced Study, Department of Chemistry, University of Delhi, for financial assistance.

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Synthesis of Dihydrocurcumin

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Dihydrocurcumin is synthesised by C-acylation of 4-O-benzylvanillylideneacetone (3b) with 4-O-benzyldihydroferulic acid chloride (2b) in the presence of NaH-THF.

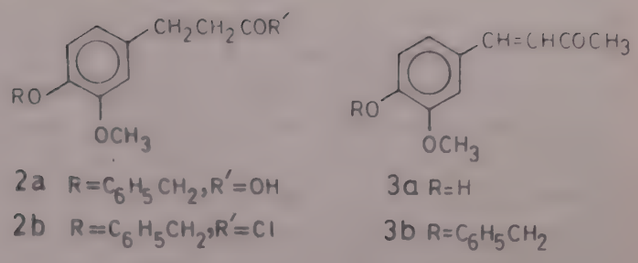
Dihydrocurcumin, isolated from the rhizomes of *Curcuma longa* as a minor component of the curcuminoids, was assigned structure (**1**) based on spectral evidences[1] and on the fact that it gives curcumin (**4**) on DDQ dehydrogenation. In connection with our ongoing project on the evaluation of curcuminoids as antioxidants and radiation modifiers, we needed **1**. The literature does not record its synthesis. We report herein the synthesis of **1**. Hydrogenation of curcumin (**4**) or partial dehydrogenation of tetrahydrocurcumin to **1** could not be achieved. The key step in the present synthesis involves the C-acylation of the benzyl ether of vanillylideneacetone (**3b**) with 4-O-benzyldihydroferulic acid chloride (**2b**). The final debenzylation of di-O-benzyl dihydrocurcumin to **1** gave poor yields and we could not find any efficient method as yet, for this purpose.

4-O-benzyldihydroferulic acid (**2a**)

A mixture of dihydroferulic acid[2] (1 g, 6 mmol), benzyl chloride (0.9 g, 1.1 equiv), dry acetone, anhydrous sodium iodide (0.93 g) and anhydrous K_2CO_3 (15 g) was refluxed for 8 hr, filtered and the precipitate washed with acetone. The combined organic extract was concentrated, the residue treated with water and extracted with ether. The total ether concentrate was subjected to alkaline hydrolysis (20%, KOH). The reaction mixture was cooled, acidified with conc. HCl and extracted with ether. The ether extract was subjected to alkaline hydrolysis (20%, KOH). The reaction mixture was cooled, acidified with conc. HCl and extracted with ether. The ether extract was washed with saturated aq. $NaHCO_3$ and the bicarbonate extract acidified with dil. HCl to yield (**2a**) as a solid which crystallized from hot water, m.p. 91-93°, yield (1.2 g, 75%) (Found: C, 71.2; H, 6.3. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.3%); IR (KBr): 1690, 1600, 1440 and 1240 cm^{-1}; PMR ($CDCl_3$): δ 2.7 (*m*, 4H, $-CH_2-CH_2-$), 3.8 (*s*, 3H, OCH_3), 5.0 (*s*, 2H, $-OCH_2-Ar$), 6.6 (*m*, 2H, Ar−H), 7.2 (*m*, 6H, Ar−H).

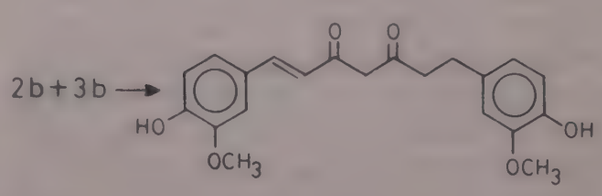
Acid chloride (**2b**)

A mixture of (**2a**, 0.5 g) and thionyl chloride (5 ml), was stirred for 12 hr at room temperature (~28°). Excess thionyl chloride was removed *in vacuo* (25°, 0.01 mm). The crude acid chloride (**2b**) was dried in a vacuum desiccator and used directly in the next step; IR (nujol): 1790 cm^{-1}.



2a R=$C_6H_5CH_2$, R'=OH
2b R=$C_6H_5CH_2$, R'=Cl

3a R=H
3b R=$C_6H_5CH_2$



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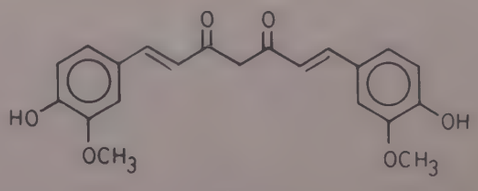

4

4-O-*benzyl vanillylidene acetone* (**3b**)

Vanillylideneacetone[3] (**3a**, 1 g, 5.2 mmol) in acetone (20 ml) was treated with benzyl chloride (0.3 g, 5.5 mmol) and the mixture refluxed for 6 hr. Usual work-up afforded a residue, which crystallized from methanol-pet. ether to yield **3b**, m.p. 92-93°, yield (78%) (Found: C, 76.4; H, 6.4. $C_{18}H_{18}O_3$ requires C, 76.6; H, 6.4%); IR (KBr): 1660, 1595, 1484, and 1420 cm^{-1}; PMR ($CDCl_3$): δ 2.3 (*s*, 3H, $-COCH_3$), 3.9 (*s*, 3H, $-OCH_3$), 5.1 (*s*, 2H, $-CH_2-Ar$), 6.5 (*d*, 1H, J=14Hz, $=CH-CO-$), 6.8-7.0 (*m*, 3H, Ar−H, $=CH-Ar$), 7.3 (*bs*, 6H, Ar−H).

Reaction between **2b** *and* **3b**

The ketone (**3b**, 1 g, 3 mmol) in anhydrous ether was cooled to 0° and treated with sodium hydride (0.09 g, 3 mmol) under N_2 atmosphere. The reaction mixture was kept stirred and the acid chloride (**2b**, 1.08 g, 3 mmol) in dry ether was added dropwise during a period of 30 minutes, the temperature maintained at 0°. After the completion of addition, the reaction mixture was allowed to attain room temperature (28-

29°), stirred for 1.5 hr at this temperature and finally refluxed for 1 hr. The cooled reaction mixture was treated with ice and dil. HCl, stirred and extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried and concentrated. The crude residue (0.8 g, 42%) was boiled with conc. HCl-HOAc (1:2 v/v) for 1 hr and cooled. The reaction mixture was diluted with water, extracted with ethyl acetate, dried and concentrated to yield a residue (0.2 g). TLC examination of the residue showed the presence of several products. The products were separated by chromatography over silica gel column using benzene as the irrigant. The fractions which gave red colour with ammonia and positive rubrocurcumin test[4] were pooled, solvent removed and the residue crystallized twice from chloroform to yield (**1**) as a pale yellow crystalline solid, yield 0.06 g, m.p. and m.m.p. 174-76°; R_f (benzene) 0.65 for both synthetic and natural samples (Found: C, 68.0; H, 6.0; Calc. for $C_{21}H_{22}O_6$: C, 68.1; H, 5.9%); IR (KBr): 3400, 1635 ($-CO-CH_2-CO$), 1600 (Ar), 1510, 1150, 1030, 860, 820 and 800 cm^{-1}; UV (EtOH): 368 (log ε, 4.30), 305 (log ε, 3.7) and 282 nm (log ε, 3.50); PMR (200 MHz, CD_3COCD_3): δ 2.6 (*t*, 2H, $J=6$Hz, $Ar-CH_2-CH_2-CO-$), 2.8 (*t*, 2H, $J=6$Hz, $Ar-CH_2-CH_2-CO-$), 3.8 (*s*, 6H, $2\times OCH_3$), 5.9 (*s*, 1H, $-C-CH=C-$), 6.5 and 7.4 (complex multiplet, 8H, olefinic and aryl hydrogens).

We thank Dr Ravindranath, CFTRI, Mysore for a sample of natural dihydrocurcumin and Department of Atomic Energy, Bombay for a fellowship (to SG).

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Studies on Coumarin Derivatives: Part I—Synthesis of Some Substituted Thiazolyl- & Benzoxazinyl-coumarins

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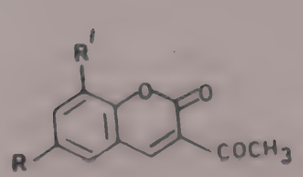
A number of thiazolyl- and benzoxazinyl-coumarins have been prepared and tested for their antibacterial and antifungal activities. None of the compounds is found to be active.



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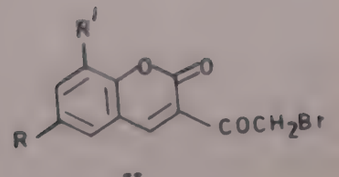

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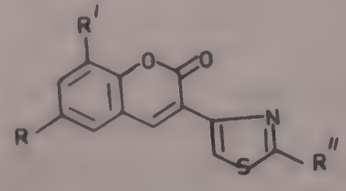

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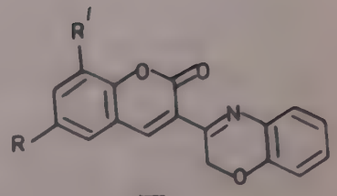

IV

Coumarins bearing one or more phenolic groups and containing pyridyl moiety at 3-position are spasmolytic and uricosuric agents[1]. Further thiazoles[2] and benzoxazines[3] possess an array of biological activities. We envisaged that incorporation of these hetero systems in a coumarin nucleus may impart enhanced biological activity to the resulting compounds. With this in view we report herein the synthesis and biological activity of a few title compounds. 3-Acetylcoumarins (Ia-e) were prepared from the corresponding salicylaldehydes by the usual procedure and the corresponding bromoacetyl derivatives (IIa-e) were prepared by reacting Ia-e with bromine (IIa is a known compound[4]). The structural assignment of IIa-e is based on their elemental analyses (Table 1) and spectral data.

Condensation of II with thioamides in either ethanol containing few drops of piperidine or anhydrous ethanol and DMF furnished 3-(2-substituted-4-

Table 1—Characterization Data of II, III and IV

Compd*	R	R′	R″	m.p.† °C	Mol. formula	Found(%)(Calc)‡ N	S
IIb	Cl	H		167	$C_{11}H_6O_3ClBr$	—	—
IIc	H	NO_2		180	$C_{11}H_6NO_5Br$	—	—
IId	Br	H		194	$C_{11}H_6O_3Br_2$	—	—
IIe	Br	Br		228	$C_{11}H_5O_3Br_3$	—	—
IIIa	H	H	CH_3	186	$C_{13}H_9NO_2S$	5.74(5.76)	13.00(13.16)
IIIb	H	OCH_3	CH_3	205(d)	$C_{14}H_{11}NO_3S$	5.10(5.12)	11.72(11.72)
IIIc	Cl	H	CH_3	160	$C_{13}H_8NO_2ClS$	5.00(5.05)	11.50(11.55)
IIId	H	NO_2	CH_3	210	$C_{13}H_8N_2O_4S$	9.70(9.72)	11.10(11.11)
IIIe	Br	H	CH_3	216-218	$C_{13}H_8NO_2BrS$	4.34(4.34)	9.90(9.93)
IIIf	Br	Br	CH_3	250	$C_{13}H_7NO_2Br_2S$	3.48(3.49)	7.90(7.98)
IIIg	H	H	Ph	165	$C_{18}H_{11}NO_2S$	4.58(4.59)	10.48(10.49)
IIIh	H	OCH_3	Ph	196	$C_{19}H_{13}NO_3S$	4.10(4.17)	9.54(9.55)
IIIi	Cl	H	Ph	128	$C_{18}H_{10}NO_2ClS$	4.12(4.12)	9.42(9.43)
IIIj	H	NO_2	Ph	262	$C_{18}H_{10}N_2O_4S$	8.00(8.10)	9.14(9.14)
IIIk	Br	H	Ph	207	$C_{18}H_{10}NO_2BrS$	3.62(3.64)	8.32(8.33)
IIIl	Br	Br	Ph	210	$C_{18}H_9NO_2Br_2S$	3.02(3.02)	6.90(6.91)
IVa	H	H		120	$C_{17}H_{11}NO_3$	5.02(5.05)	—
IVc	Cl	H		232(d)	$C_{17}H_{10}NO_3Cl$	4.40(4.50)	—
IVd	H	NO_2		218	$C_{17}H_{10}N_2O_5$	8.66(8.69)	—
IVe	Br	H		250	$C_{17}H_{10}NO_3Br$	3.92(3.93)	—
IVf	Br	Br		230	$C_{17}H_9NO_3Br_2$	3.20(3.21)	—

*Compounds IIb-e were obtained in 70-76% yield, IIIa-l in 60-70%, and compounds IVa-IVf in 40-50%.
†Solvents for crystallisation were: AcOH for IIb,c,d,e; methanol for IIIa-l and for IVa-f.
‡Satisfactory C, H analyses were obtained.

thiazolyl)-2H-1-benzopyran-2-ones (IIIa-l); however the second method gave the products in good yields. The structures of IIIa-l were in conformity with their elemental analyses (Table 1) and characteristic spectral data. IR spectra of the thiazolylcoumarins(IIIa-l) exhibited peaks at 1720-1730 due to lactone carbonyl of coumarin and strong bands at 1500, 1580 and 1605 cm^{-1}, characteristic of thiazole ring system[5]. The PMR ($CDCl_3$) spectrum of IIIa exhibited signals at δ 2.65 (*s*, 3H, $-CH_3$), 7.3-7.62 (*m*, 4H, aromatic protons of coumarin ring), 8.25 (*s*, 1H, $C_{5'}-H$ of thiazole ring) and 8.64 (*s*, 1H coumarin C_4-H) while that of IIIg in $CDCl_3$ displayed signals at δ 7.05-7.50 (*m*, 4H, aromatic protons of coumarin ring), 7.80-7.90 (*m*, 5H, Ar−H), 8.25 (*s*, 1H, $C_{5'}-H$ of thiazole) and 8.60 (*s*, 1H, coumarin C_4-H). The mass spectrum of 3-(2-methyl-4-thiazolyl)-2H-1-benzopyran-2-one (IIIa) showed the molecular ion peak at *m/z* 243 as the base peak and other peaks at *m/z* (rel. intensity) 215 (18%, M^+-CO), 174 (42%), 202 (36%), 146 (20%), 145 (21%) and 102 (44%).

A convenient one step synthesis of 3-(2*H*-1,4-benzoxazin-3-yl)-2H-1-benzopyran-2-ones (IV) has been achieved by the reaction of 2-aminophenol with 3-(ω-bromoacetyl)coumarins. The 2-aminophenoxy-acetylcoumarin derivatives formed as intermediates undergo spontaneous cyclization *in situ* under the reaction conditions. The structure of the products were supported by their elemental analyses and spectral data.

Biological activity of IIIa-l

All the thiazolylcoumarins (IIIa-l) were screened for their antibacterial[6] and antifungal[7] activity at concentration of 400-600 μg/ml against *Esch. coli* and *Bacillus magaterium* and *Curvularia lunata* and *Dreschlera halodes*, respectively. None of the compounds showed any marked activity.

All the melting points reported are uncorrected. The purity of the compounds was checked by TLC using silica gel-G as stationary phase and benzene-methanol as the mobile phase.

8-*Methoxy*-3-(ω-*bromoacetyl*)*coumarin* (*IIa*)

To a solution of 8-methoxy-3-acetylcoumarin (0.025 mol) in alcohol-free chloroform (40 ml) was added bromine (0.025 mol) in chloform (2.5 ml) with thorough shaking and warming. The mixture was heated for about 15 min on a water-bath to expel most of hydrogen bromide. The solid was washed with ether, recrystallized from acetic acid to give IIa, m.p. 206°, yield 78% (Found: C, 48.7; H, 3.0. $C_{12}H_9O_4Br$ requires C, 48.5; H, 3.0%); IR: 755 (−C−Br), 1685 (−C=O, $-COCH_2Br$) and 1720 (lactone carbonyl of coumarin); PMR (DMSO-d_6): 3.85 (*s*, 3H, $-OCH_3$), 4.25 (*s*, 2H, $-COCH_2Br$), 7.2-7.45 (*m*, 3H, aromatic) and 8.75 (*s*, 1H, coumarin C_4-H).

Following the above procedure the remaining bromo compounds have been prepared. Their physical and analytical data are listed in Table 1.

3-(2-*Substituted*-4-*thiazolyl*)-2*H*-1-*benzopyran*-2-*ones*

These were prepared by two different methods. (a) A mixture of II (0.01 mol) and thioamide (0.01 ml) in ethanol (15 ml) containing a few drops of piperidine was refluxed for about 6 hr, cooled, the solid separated filtered, washed thoroughly with water and crystallised from suitable solvents to afford III in 50-60% yields. (b) A mixture of II (0.01 mol) and thioamide (0.01 mol) in anhydrous ethanol (15 ml)+DMF (15 ml) was refluxed for about 4 hr, cooled, the solid separated filtered, washed thoroughly with water and crystallised from suitable solvents to afford III in 60-70% yield;

Mass: *m/z* (*rel. intensity*) − 335 (M^+, 100%), 307 (15%), 264 (10%), 232 (10%), 204 (20%), 161 (30%) *and* 89 (30%)

3-(2*H*-1,4-*Benzoxazin*-3-*yl*)-8-*methoxy*-2*H*-1-*benzopyran*-2-*one* (*IVb*; *R'* = *OMe*; *R* = *H*)

To a solution of *o*-aminophenol (1.09 g; 0.01 mol) in dry acetone (150 ml), anhydrous potassium carbonate (0.015 mol) was added and the mixture stirred for 3 hr at room temperature. To this mixture were added IIa (2.97 g; 0.01 mol) and additional potassium carbonate (0.015 mol) and the resultant mixture refluxed for 18 hr. The reaction mixture was filtered and inorganic material washed with fresh acetone. The combined organic extract was concentrated *in vacuo* and the residue was triturated with hot water to remove the unreacted *o*-aminophenol. The solid thus obtained was filtered and crystallized from methanol to furnish IVb as yellow crystals; yield 1.22 g (40%), m.p. 222° (Found: C, 70.3; H, 4.2; N, 4.5. $C_{18}H_{13}NO_3$ requires C, 70.3; H, 4.2; N, 4.6%); IR: 1605 (−CN−) and 1710 (lactone carbonyl); PMR ($CDCl_3$): 2.15 (*s*, 3H, OCH_3), 4.04 (*s*, 2H, $-CH_2-$), 7.00-7.44 (*m*, 7H, aromatic) and 7.84 (*s*, 1H, coumarin C_4-H).

Other 3-(2H-1,4-benzoxazin-3-yl)-2H-1-benzopyran-2-ones were prepared similarly.

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Isolation of a New Flavanone & Lanceolatin-B from *Lannea acida* (Rich)

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A new flavone, 7,2'-dimethoxy-4',5'-methylenedioxyflavone (**1**) and the known lanceolatin-B (**2**) have been isolated from the leaves of *Lannea acida* (Rich).

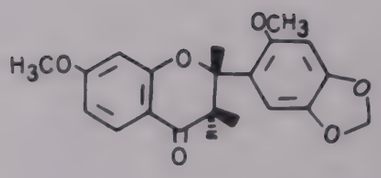
In a broad programme on the flavonoid constituents of plant species, we undertook the chemical examination of the leaves of *Lannea acida* (Rich). We have been able to isolate a new flavanone (compound-A) and lanceolatin-B (compound-B), the full characterisation of which by spectral data is reported in this note.

Compound-A eluted from silica gel column with benzene-ethyl acetate (7:3) and responded to usual colour tests for flavanones[1,2]. Its UV spectrum in MeOH exhibited peaks at 294 and a shoulder at 360 nm typical of an isoflavone or a flavanone[3]. However, its optical activity ($[\alpha]_D - 19.1$) favoured a flavanone structure.

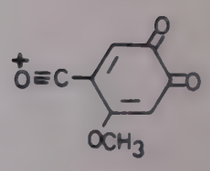
The PMR spectrum of compound-A displayed two singlets at δ 3.85 (3H) and 4.0 (3H) assignable to two methoxyl groups and a two-proton singlet at δ 6.0 due to methylenedioxy protons. A doublet at δ 8.0 ($J = 9$Hz) for H-5 proton indicated the absence of substitution at C-6. The appearance of H-6 as a double doublet at δ 7.6 ($J = 9$Hz and 2Hz) indicated that C-8 was also unsubstituted. H-8 appeared as a doublet at δ 7.45 ($J = 2$Hz). Two protons of B-ring appeared as two one-proton singlets at δ 6.5 (3'-H) and 7.1 (6'-H). In the mass spectrum of compound-A the molecular ion peak appeared at m/z 328 (27%), the other peaks at m/z 165 (base peak) and 178 corresponding to the ions (**2**) and (**3**) respectively.

On the basis of above data the compound is formulated as 7,2'-dimethoxy-4',5'-methylenedioxy-flavanone (**1**).

Compound-B was eluted with benzene-ethyl acetate (1:7), white needles (benzene-methanol), m.p. 138-40°; UV (MeOH): 261 and 295 nm; IR (Nujol): 1665 (C=O), 690 and 755 cm^{-1} (characteristic of unsubstituted phenyl); PMR (60MHz, $CDCl_3$): δ 6.87 (1H, s, 3-H), 7.2 (1H, *d*, β-furan proton), 7.76 (1H, *d*, α-furan proton), 8.2 (1H, *d*, $J = 10$ Hz, 5-H), the doublet of the C-6 proton is lost in the multiplet at 7.56. It analysed for $C_{17}H_{10}O_5$ (M^+ 262, 60%) and in its mass spectrum peaks corresponding to fragments $C_9H_4O_3$ (**5**) and C_8H_6 (**6**), formed through the retrodene cleavage, confirmed the compound-B as lanceolatin-B[4] (**4**).



(1)



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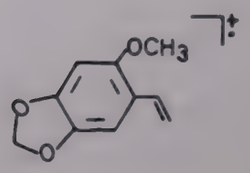

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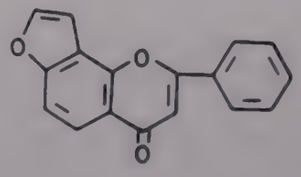

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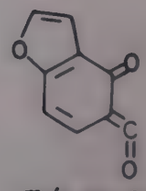
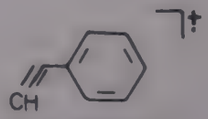


m/e 160 (100)

(5)



m/e 120 (8·2)

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Vicolide-D, a New Germacranolide from *Vicoa indica* DC

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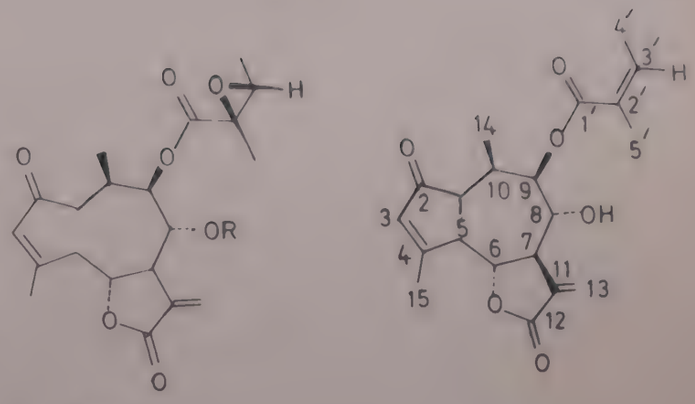
Vicolide-D, a new germacranolide isolated from *Vicoa indica* DC is shown to be 2',3'-epoxyvicolide-B (I) by chemical and spectroscopic evidences

In a previous communication Purushothaman *et al.*[1] reported the isolation of three sesquiterpenoid lactones, viz. vicolides A, B and C from the plant *Vicoa indica*. Herein we report the isolation and structure elucidation of yet another lactone, vicolide-D from this plant.

The chloroform extract of the air-dried and powdered plant (5 kg) was concentrated under reduced pressure and the residue subjected to column chromatography over silica gel. Benzene-ethyl acetate (1:1) eluate yielded vicolide-D (100 mg) (I), which crystallised from methanol, m.p. 214-16°, $C_{20}H_{26}O_7$, $[\alpha]_D -80°$ (*c*, 1 in $CHCl_3$); *m/z* 378(M^+); IR: 1775 (γ-lactone), 1730(ester CO) and 1685 cm^{-1} (α,β-unsaturated ketone). The molecular weight of vicolide-D (I) differed from that of vicolide-B (III) by 16 mass units. Further, I had an extra oxygen atom in its molecular formula. The PMR spectrum of vicolide-D (chemical shifts in δ-scale downfield from TMS internal reference) revealed the following functionalities: an exomethylene (5.77 and 6.44, *d* each, $J=3$Hz, 2H-11), an olefinic proton (6.30, *bq*, $J=1$Hz, H-3), two secondary methyls (1.06, *d*, $J=7$Hz, 3H-14; 1.35, *d*, $J=5.5$Hz, 3H-4'), a tertiary methyl (1.60, *s*, 3H-5'), a vinylic methyl (1.90, *d*, $J=1$Hz, 3H-15), a proton attached to carbon carrying ester moiety (5.30, *dd*, $J=2.5$ and 10.5Hz, H-9) and a hydroxyl proton (2.04, D_2O exchangeable). In general, it exhibited almost the same PMR characteristics of vicolide-B for a germacranolide skeleton. But there were some salient distinguishing features in the ester side chain. The olefinic proton at 6.15 in the angeloyl side chain of vicolide-B was absent in vicolide-D. Instead a quartet at 3.02 ($J=5.5$Hz) was noticed. The secondary and tertiary eethyls of the side chain in vicolide-D appeared at 1.35(*d*, $J=5.5$Hz) and 1.60 (*s*) respectively. In vicolide-B secondary and tertiary methyls appeared at 2.00 (*dq*, $J=7.3$ & 1.5Hz) and 1.94 (*dq*, $J=1.3$ & 1.5Hz). These observations are reminiscent of an epoxy



I R=H
II R=Ac

III

function in the ester side chain, and its tri-substituted nature was quite evident from the ^{13}C NMR signals at δ 60.1(*d*) and 59.6(*s*). The region between 2.6 and 3.3 in the PMR spectrum integrated for six protons in vicolide-D instead of five in vicolide-B.

Vicolide-D gave a monoacetate(II), m.p. 185-88°, $C_{22}H_{28}O_8$. Its mass spectral fragment at *m/z* 304 indicated the loss of $C_5H_8O_3$ moiety (M^+-116), corresponding to 2,3-epoxy-2-methylbutanoyl moiety. The fragment at *m/z* 244 (base peak) indicated a sequential or simultaneous Mc-Lafferty rearrangement of the side chains from C-9 (epoxy angelic acid, 116 a.m.u.) and C-8 (acetic acid from 60 a.m.u.) in vicolide-D acetate. The other PMR and ^{13}C NMR characteristics were similar for both the acetates. These foregoing data established the structure of vicolide-D to be 2',3'-epoxyvicolide-B. This was further confirmed by the epoxidation of vicolide-B with *m*-chloroperbenzoic acid (1:1 mol proportion) to vicolide-D [identical (co-TLC, m.m.p., co-IR) with the natural sample] as the major product. Therefore, structure (I) has been assigned to vicolide-D in analogy with vicolide-B.

The configuration of the disymmetric atoms at 2' and 3' is 2'R and 3'R in analogy with melampodin[2]. In the naturally occurring germacranolides, the epoxy angeloyl group has a β-epoxide configuration as exemplified by melampodin, uvedalin[3], leucanthinin[4] and eupacunoxin[5], and in conformity with the above cited examples the epoxide in vicolide-D is also assigned β-configuration.

Our thanks are due to Dr J D Connolly, Department of Chemistry, University of Glasgow, UK for spectroscopic data, to the Central Council for Research in Ayurveda and Siddha for financial support

and to (Mrs) P Brindha for the collection of plant material.

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O→N Benzoyl Migration During Catalytic Hydrogenation of Benzyl Benzoyloxymethyl Ketooximes

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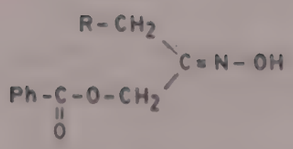
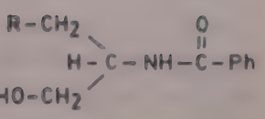
Catalytic hydrogenation of oximes (I-V) over Raney nickel yields the N-benzoylaminoalcohols (VI-X), instead of the expected amines.

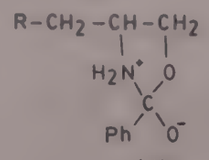


(I-V)

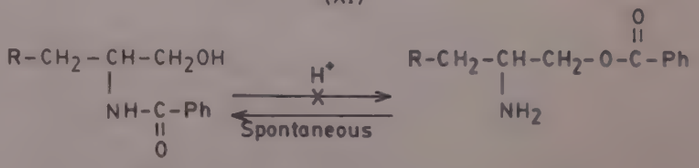


(VI-X)

(I), (VI): R = Ph; (II), (VII): R = p-H_3COPh;
(III), (VIII): R = p-ClPh; (VI), (IX): R = p,m-$(H_3CO)_2$Ph;
(V), (X): R = p-H_3CPh



(XI)



(B) (A)

In the context of our studies on the preparation of amines[1,2], we envisaged that the catalytic reduction of oximes (I-V) over Raney nickel would yield the corresponding amines. However, we found that the reduction was accompanied by rearrangement leading to the formation of 2-benzoylamino-3-arylpropanols (VI-X) (Table 1).

Structures of VI-X are based on elemental analyses and spectral data. IR spectra of VI-X exhibited strong bands in the region 1625-1645 cm^{-1} due to $\nu C=O$ (amide). The PMR spectra displayed doublets at δ 2.90-2.97 (2H, CH_2-Ph) and 3.63-3.72 (2H, CH_2-O). The methine proton separating CH_2-Ph and CH_2-O groupings and attached to amide nitrogen was seen as a multiplet in the region 4.28-4.40. The NH and OH protons, which appeared in the regions 4.30-4.40 and 3.15-3.28 respectively were found to be exchangeable with D_2O.

Evidently the products (VI-X) are formed by the migration of the benzoyl group. Towards rationalisation of product formation, we believe that the oxime is first converted into amine, which then attacks the CO of the benzoyloxy group to form a five-membered hydroxyoxazolidine-type of system (XI). This system being unstable, undergoes cleavage in a fashion analogous to the hypothetical five-membered ring intermediate proposed by Phillips and Baltzly[3], to yield the rearranged products. Such a rationalisation is supported by the following observations.

Attempts to prepare 1-benzoyloxy-2-amino-3-arylpropanes (A) by treatment of products (B) with 5%

Table 1—Characterization Data of Oximes (I-V) and 2-Benzoylamino-3-arylpropanols (VI-X)

Oximes (I-V)*		Aminoalcohols (VI-X)*				
m.p. (°C)	Mol. formula	m.p. (°C)	Mol. formula (M⁺)	Found (%) (Calc.)		
				C	H	N
86	$C_{16}H_{15}NO_3$	148-49	$C_{16}H_{17}NO_2$ (255)	75.32 (75.29	6.65 6.67	5.52 5.50)
87	$C_{17}H_{17}NO_4$	116	$C_{17}H_{19}NO_4$ (285)	71.55 (71.58	6.62 6.67	4.85 4.91)
111	$C_{16}H_{14}ClNO_3$	136	$C_{16}H_{16}ClNO_2$ (289)	66.40 (66.44	5.53 5.54	4.85 4.84)
Oil	$C_{18}H_{19}NO_5$	134-35	$C_{18}H_{21}NO_4$ (315)	68.52 (68.50	6.68 6.67	4.40 4.44)
101	$C_{17}H_{17}NO_3$	125	$C_{17}H_{19}NO_2$ (269)	75.88 (75.84	7.00 7.06	5.20 5.20)

*All the oximes and N-benzoylaminoalcohols in this paper are reported for the first time.

hydrochloric acid through a possible N→O migration[4,5] could not succeed. This may be due to the fact that NH_2 in (A) is more basic than OH in (B), and on analogy with the observation of Selwitz and Kosak[6], reacts with CO of benzoyloxy group no sooner it is produced during the reaction and therefore the backward reaction is favoured to give exclusively (B).

The melting points are uncorrected. The oximes (I-V) were prepared by the reaction of respective ketones with $NH_2OH.HCl/Na_2CO_3$ at room temperature and these were fully characterised by elemental analysis and spectral data.

Catalytic hydrogenation of oximes (*I-V*): *Formation of* 2-*benzoylamino*-3-*arylpropanols* (*VI-X*)

A mixture of oxime (1 g), methanol (40 ml) and freshly prepared Raney nickel (~1.5 g) was hydrogenated at 25-30 psi for 3-4 hr. The progress of the reaction was monitored by TLC. The suspension was filtered and the solvent removed on a water-bath to get an oily residue, which was crystallized from ethanol-chloroform (5:1); yield 60-70%.

The authors are grateful to Prof. M.S. Ahmad, for encouragement, and to CSIR, New Delhi for financial assistance to two of us (SSN and MH).

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Use of Anion Exchange Resin in Synthesis of Aryloxyacetic Acid Esters

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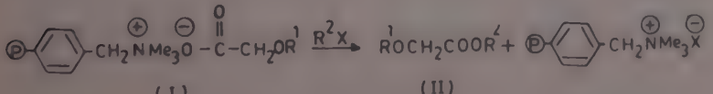
Insoluble polymer-supported nucleophilic reagent has been prepared by treatment of sodium salt of aryloxyacetic acid with Amberlite IRA-400 (Cl^-). This reagent has been used for the synthesis of aryloxyacetic acid esters in high yields by reaction with alkyl halides. In addition to ease and simplicity of the method and regeneration of the polymeric by-product, the polymeric reagent seems to increase the nucleophilicity of the anions. In addition to this, transesterification is observed when alcohol is used as the solvent.

Aluminium chloride[1] supported on a polymer matrix such as polystyrene, (P)-$AlCl_3$, is a mild catalyst for esterification and has the advantage of being both a Lewis acid and a dehydrating agent. Insoluble polymer-bound nucleophilic reagent derived from poly(vinylbenzyltriphenylphosphonium chloride) has been used for the synthesis of carboxylic acid esters[2]. In continuation of our work on polymer-supported reactions[3] and in view of the importance of aryloxyacetic acid esters as flavouring agents, a simple and efficient method is now reported for esterification of aryloxyacetic acids.

Reaction of sodium salt of aryloxyacetic acid with Amberlite IRA-400 (Cl^--form) forms the polymer-supported aryloxyacetate ion(I) which can be alkylated by treatment with alkyl halide (R^2X) in a suitable solvent. The products(II) are obtained in higher yields



(I) (II)

and in state of high purity. The results are summarised in Table 1. The esterification can be carried out both in polar and nonpolar solvents, showing that the reaction is independent of the nature of the solvent. This implies that less expensive and less poisonous solvents may often be employed. Runs with catalytic amount of the resin do not give satisfactory results, indicating that the nucleophilicity of polymer-bound aryloxyacetate ion is increased sufficiently to allow esterification with alkyl halides in a manner which, in principle, is akin to phase transfer catalysis with low molecular weight catalysts.

Table 1 — Alkylation of Polymer-supported Aryloxyacetate Ion to Give Esters at 25°C

R^2X	Solvent	Reaction period (hr)	Yield (%)
	$R' = C_6H_5$-		
CH_3I	Benzene	4	92
C_2H_5I	do	5	90
CH_3I	1,2-Dimethoxyethane	4	90
C_2H_5I	do	5	91
CH_3I	Methanol	5	94
C_2H_5I	Ethanol	5	93
$CH_2=CHCH_2Br$	Benzene	12	60
n-C_4H_9Br	do	15	65
	$R' = o$-$CH_3C_6H_4$-		
CH_3I	Benzene	6	87
C_2H_5I	do	6	85
	$R' = m$-$CH_3C_6H_4$-		
CH_3I	Benzene	6	90
C_2H_5I	do	6	85
	$R' = p$-$CH_3C_6H_4$-		
CH_3I	Benzene	5	85
C_2H_5I	do	5	83
CH_3I	do	4	90
C_2H_5I	do	4	97

In addition to this transesterification is observed when alcohol is used as a solvent. For example I ($R^1 = C_6H_5$) when stirred with methyl iodide in ethanol for 12 hr, afforded after work-up, the ethyl ester, $C_6H_5OCH_2COOC_2H_5$, in 86% yield. This reaction of I ($R^1 = C_6H_5$) with ethyl iodide in methanol afforded the corresponding methyl ester, $C_6H_5OCH_2COOCH_3$ in 87% yield.

General procedure for preparation of polymer-supported aryloxyacetic acid anion(I)

Amberlite IRA-400 in the chloride form was packed in a column, which was eluted with 0.25 *N* aqueous sodium salt of aryloxyacetic acid (prepared by dissolving 25 mmol of aryloxyacetic acid in 100 ml 0.25 *N* NaOH) until complete removal of chloride ion. The resin was successively washed with water and acetone and dried *in vacuo* at 50° over P_2O_5 for 5 hr. The exchange capacity was determined by passing aqueous 1 *M* sodium chloride solution (100 ml) through the resin (0.3 g) in a column and the amount of aryloxyacetic acid anion in the eluent was titrated against 0.01 *N* hydrochloric acid using methyl orange as an indicator.

General procedure for O-alkylation of aryloxyacetic acids

To the above polymer-supported aryloxyacetate ion (5 g, 1 mmol of aryloxyacetic acid anion/g of dry resin) in the desired solvent was added a solution of alkylating agent (20 mmol) in the same solvent and the mixture stirred for periods mentioned in Table 1. The resin was filtered off and the filtrate slowly distilled under reduced pressure to remove the solvent and excess of alkylating agent. The products obtained in high yields were essentially pure and were characterised by their spectral data (PMR, IR) and comparison with authentic samples.

One of us (BPB) is grateful to the UGC, New Delhi for financial assistance under the Faculty Improvement Programme.

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Phenyl Isothiocyanate-Mediated Cyclocondensation of Hippuric Acid in Presence of Salicylaldehyde/*o*-Hydroxyacetophenone

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Hippuric acid (**1**), when heated with phenyl isothiocyanate (**2**) and salicylaldehyde (**3a**) at 170° for 30 min, affords 3-N-benzoylaminocoumarin (**4a**) and (*Z*)-4-(*o*-hydroxybenzylidene)-1,2-diphenyl-2-imidazolin-5-one (**5**). *o*-Hydroxyacetophenone affords hippuranilide as the main product, though **4b** is discernible by TLC.

N-Alkyl- and N-aryl-isothiocyanates react with carboxylic acids to afford N-substituted amides[1]. We have recently proposed that N-acyl-α-amino acids undergo cyclocondensation to 2-oxazolin-5-ones, on heating with phenyl isothiocyanate, followed by aminolysis with the generated aniline[2]. The title investigation has been undertaken to verify this proposition.

Thus, when hippuric acid (**1**) and phenyl isothiocyanate (**2**) were heated together at 160-70° for 30 min in the presence of salicylaldehyde (**3a**) with pyridine as a catalyst, the compounds isolated after usual work-up were identified as 3-benzoylamino-coumarin (**4a**), yield 34%, m.p. 175-76° (lit[3,4] m.p. 175°) and 4-(*o*-hydroxybenzylidene)-1,2-diphenyl-2-imidazolin-5-one (**5**), yield 10%, m.p. 208-10°; IR: 3400, 1710; 1630 cm^{-1} (Found: C, 73.4; H, 4.7; N, 7.7. $C_{22}H_{16}N_2O_2.H_2O$ requires C, 73.7; H, 5.0; N, 7.8%).

Under similar conditions, using *o*-hydroxyacetophenone (**3b**), instead of **3a**, the major product isolated was hippuranilide (59%), m.p. 210-12° (lit.[5] m.p. 209-11°). 3-Benzoylamino-4-methylcoumarin (**4b**) could not be isolated but was detected by co-TLC with an authentic specimen. The formation of these compounds can be rationalised only by assuming 2-oxazolin-5-one (**6**) as an intermediate.

The proof of the intermediacy of **6** in the formation of **5** was provided by synthesising **5** starting from 4-(*o*-acetoxybenzylidene)-2-phenyl-2-oxazolin-5-one (**7**, $R^1 = H$; $R^2 = Ac$), which in turn was prepared by the condensation of *o*-acetoxybenzaldehyde (**3c**) and **6**. The pure (*Z*)-isomer **7** ($R^1 = H$, $R^2 = Ac$) was separated by fractional crystallisation[3] and subjected to aminolysis under different conditions. On heating it with aniline in glacial acetic acid, in the presence of catalytic amount of fused sodium acetate for about 4 hr, **5** and acetanilide were obtained. It is noteworthy that when **7** and aniline were heated together, without using any solvent, the main product isolated was identified as N-phenyl-2-benzoylamino-*o*-acetoxy-cinnamide (**8**). On increasing the proportion of aniline, the yield of **8** decreased, indicating partial O-deacetylation. Though formation of **5** in this case was indicated by TLC, it could not be isolated. It should be mentioned that aminolysis of the coumarin (**4**) with aniline was unsuccessful, thereby ruling out the possibility of **4a** as an intermediate in the formation of **5**.

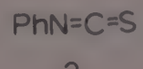
The products reported in this article were characterised by spectral and elemental analyses and by comparison with authentic samples.

Reported melting points are uncorrected. IR spectra in nujol were recorded on Perkin-Elmer 720 model.

Authentic 4-(*o-hydroxybenzylidene*)-1,2-*diphenyl*-2-*imidazolin*-5-*one* (**5**)

An equimolar mixture of (*Z*)-4-(*o*-acetoxybenzoyli-

1



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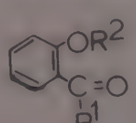
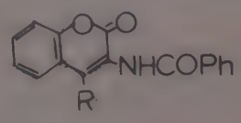
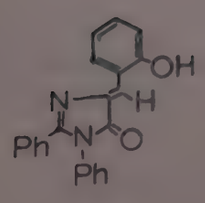


3 a $R^1 = R^2 = H$
b $R^1 = Me$; $R^2 = H$
c $R^1 = H$; $R^2 = Ac$



4 a R = H
b R = Me



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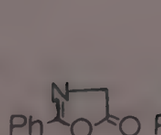

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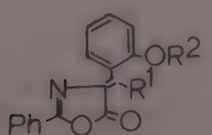

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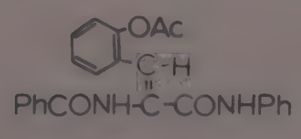

8

dene)-2-phenyl-2-oxazolin-5-one (**7**, $R^1 = H$; $R^2 = Ac$)[4] [prepared by the condensation of 2-phenyl-2-oxazolin-5-one (**6**) and *o*-acetoxybenzaldehyde, taken in the molar ratio of 1:1, according to literature method[7]], and aniline in glacial acetic acid, containing catalytic amount of freshly fused sodium acetate, was heated under reflux for 4 hr and concentrated on a water-bath. The residue was triturated with cold ethanol and the solid obtained recrystallised from ethanol to afford **5**, yield 28%, m.p. 208-210°, indentical with the compound (**5**) obtained in the reaction of hippuric acid, phenyl isothiocyanate and salicylaldehyde in the presence of pyridine.

The filtrate on concentration and extraction with hot water afforded acetanilide, yield 36%, m.p. and m.m.p. 114°.

N-Phenyl-2-benzoylamino-o-acetoxycinnamide (**8**)

An equimolar mixture of **7** ($R^1 = H$; $R^2 = Ac$) and aniline, was heated on an oil-bath at 160-70° for 30 min. After cooling, the mixture was treated with benzene, the solid obtained filtered and recrystallised from ethanol to afford **8**, yield 37%, m.p. 183-85°; IR: 3220, 1760, 1660, 1640 cm^{-1} (Found: C, 72.1; H, 5.1; N, 7.0. $C_{24}H_{20}N_2O_4$ requires C, 72.0; H, 5.0, N, 7.0%).

We thank the CSIR, New Delhi, for the award of a junior research fellowship to one of us (R A).

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Reaction of Potassium Salts of Boc-amino Acids with *p*-Bromomethylbenzoyl Polyethylene Glycol Monomethyl Ether Catalyzed by 18-Crown-6

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18-Crown-6 has been found to be a good catalyst in the quantitative esterification of *p*-bromomethylbenzoyl polyethylene glycol monomethyl ether by the potassium salts of Boc-amino acids under mild reaction conditions while DMF is the best solvent for this reaction.

In the synthesis of peptides by the liquid-phase procedure of Bayer and Mutter[1], the first step involves attachment of an N-protected amino acid to *p*-bromomethylbenzoyl polyethylene glycol to form a benzyl ester. Several common methods of esterification involving the use of triethylammonium salts of amino acids in refluxing ethanol[2], the modified Loffett procedure involving the reaction of tetramethylammonium salt in DMF at room temperature[3] and the method of Gisin utilizing the cesium salts of Boc-amino acids in DMF at 50° have also been employed for carrying out the above reactions. Complete reaction of bromomethyl group (quantitative esterification) is usually desirable in order to avoid side reactions[4] or the reaction of amino acid side chain[5] with any remaining bromomethyl groups; however, only the cesium salt method results in a nearly quantitative esterification.

The ability of crown ethers to bind cations is well documented by several recent reviews[6]. this often allows the corresponding anionic component to function as an improved nucleophile. Regarding esterification the report of Liotta *et al.*[7] is notable which states that the complex of 18-crown-6 and potassium acetate reacts quantitatively with benzyl bromide in acetonitrile at 25° to form benzyl acetate, and little or no reaction occurs in the absence of crown ether. Although Gisin found that cesium salts of Boc-amino acids are more reactive with chloromethyl resin than other alkali metal salts[4], it is advisable to use potassium salts because they have higher association constants with crown ethers that are readily available.

We report herein the use of 18-crown-6 as catalyst in the quantitative displacement of bromide from *p*-bromomethylbenzoyl polyethylene glycol by the potassium salts of Boc-amino acids in DMF under mild conditions.

The effect of 18-crown-6 as a catalyst on the percent incorporation of Boc-amino acid potassium salts into *p*-bromomethylbenzoyl polyethylene glycol monomethyl ether was confirmed by carrying out the esterification reaction in the presence of 18-crown-6 and in the absence of it under identical conditions using different amino acids. The results are summarized in Table 1.

Studies were carried by varying the solvent, temperature, reaction period and molar ratio of the reactants in order to determine the effect of each factor on the percent incorporation of Boc-amino acids into *p*-bromomethylbenzoyl polyethylene glycol monomethyl ether, the optimum conditions and the best solvent for quantitative esterification.

The reactions carried out between Boc-amino acids and the polymer in different solvents (benzene, CH_2Cl_2 and DMF) using 1 equiv. each of 18-crown-6 and the potassium salts of different amino acids (Boc-Val, Boc-Asn and Boc-Trp) and 0.5 equiv. of the polymer at room temperature for 18 hr, showed that the incorporation values in DMF were Boc-Val(100%),

Table 1—Comparison Between the Per cent Incorporation of Boc-amino Acids into *p*-Bromomethylbenzoyl Polyethylene Glycol Monomethyl Ether in the Presence of 18-Crown-6 as a Catalyst and the Absence of it {Reaction Conditions (Gisin Reaction Conditions)—Ratio of Equivalent : Polymer-Crown Ether-Boc-amino Acid (0.5 : 1 : 1); Solvent: DMF; Temperature: 60 C; Reaction period: 48 hr}

Boc-amino acid	Incorporation of Boc-amino acid (%)	
	Without 18-crown-6	With 18-crown-6
Boc-Val	85	100
Boc-Asn	55	100
Boc-Ala	72	100
Boc-Gly	72	100
Boc-Met	44	100
Boc-Arg*	28	75.6

*Boc-Arg was used without any protecting group on the guanidine portion.

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Boc-Asn (67.3%) and Boc-Trp (99%) hese results point out that DMF is the most suitable solvent for this reaction.

Since DMF was the best solvent for the reaction, studies were carried out in DMF by varying temperature, reaction period and molar ratio between the reactants using the above mentioned amino acids. The results indicated that at room temperature after 18 hr, Boc-amino acid potassium salts could displace all the bromide if 2 equiv. of 18-crown-6, 1 equiv. of the potassium salt of Boc-amino acid and 0.5 equiv. of *p*-bromomethylbenzoyl polyethylene glycol monomethyl ether were used.

The Boc-amino acids were synthesized following the Schnable methods[8,9].

Boc-amino acid potassium salts[10]

The appropriate Boc-amino acid was dissolved in a mixture of EtOH (6 ml), H_2O (4 ml) and 1 equiv. of 1 *N* KOH solution and the solvent removed by azotropic distillation in the presence of toluene and dried *in vacuo* over P_2O_5. The resultant hydroscopic white salt was used without further treatment.

p-Bromomethylbenzoyl polyethylene glycol monomethyl ether

Polyethylene glycol monomethyl ether (50 g, 10mmol) and *p*-bromomethylbenzoyl chloride[11,12] (7g, 30mmol) were dissolved in dry toluene (500 ml) and the reaction mixture was refluxed under nitrogen atmosphere for 24 hr. The excess of toluene was distilled *in vacuo* till the total volume became 60 ml. After cooling, the product was crystallized by dropwise addition of dry ether under vigorous stirring. It was filtered, redissolved in methylene chloride and reprecipitated with dry ether. This process was repeated twice to get clear crystals, TLC: R_f in *n*-butanol-acetic acid-water (30:10:10).

The authors wish to express their sincere gratitudes to Prof. Dr Ernst Bayer for his interest and advice during this work and also for amino acid analysis.

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Synthesis of Amino Derivatives of Ursolic Acid

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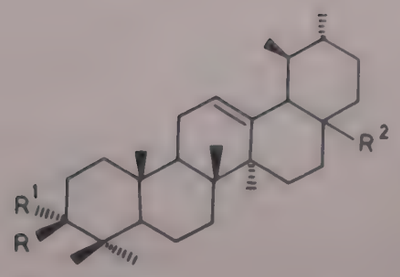
Methyl ester of 3β-amino-18β-H-urs-12-en-28-oic acid (VI) has been obtained from methyl ursolate (II) by oxidation with Kiliani reagent (CrO_3) to methyl ursonate (IV) followed by treatment of IV with NH_2OH/HCl and reduction of the resultant oxime (V) with alkali metal in 1-propanol. Refluxing of acetylursolic acid (III) with thionyl chloride followed by treatment with dry ammonia gas yields the amide (VII) which on LAH reduction affords 3β-acetoxy-18β-H-urs-12-en-28-methyl amine (VIII). Compound III on Curtius rearrangement gives 28-amino-3β-acetoxy-18β-H-urs-12-ene (IX).

It is known that introduction of an amino function in steroids alters their biological activity significantly[1] and also that synthetic and naturally occurring 3-aminosteroids possess important biological properties such as CNS, anaesthetic and neuromuscular blocking activities[2]. Further, ursolic acid (I) is a well known antiinflammatory, antibiologic, antiarthritic, antiulcer and hypolipidemic agent[3]. In this note we report the synthesis of the methyl ester of 3β-amino-18β-H-urs-12-en-28-oic acid (VI), 3-acetoxy-18β-H-urs-12-en-28-methyl amine (VIII) and 28-amino-3-acetoxy-18β-H-urs-12-ene (IX) starting from I[4]. This work was taken up with the aim of studying the variation in the biological activity and possibility of finding new activities which may be exhibited by aminosteroids.

Ursolic acid (I) was esterified with ethereal diazomethane to give methyl ursolate (II; m.p. 169-70°; lit.[5] m.p. 171°), and acetylated to yield acetylursolic acid (III; m.p. 289-90°; lit.[5] m.p. 289-90°). Methyl ursolate (II) on oxidation with Kiliani reagent afforded methyl ursonate (IV; m.p. 192-93°; lit.[6] m.p. 192-94°) which was converted into the oxime derivative (V; m.p. 244-45°; lit. m.p. 243-44°) with $NH_2OH.HCl$/pyridine. The oxime (V) was reduced with Na/*n*-PrOH to yield the methyl ester of 3β-amino-18β-H-urs-12-en-28-oic acid (VI). This synthesis is based on the known preference for the generation of equatorial amino function from the reduction of oxime (V) with Na and ethanol[8].

The above conclusion was arrived at by the fact that the PMR signal for the equatorial methine proton of the $>CHNH_2$ group appears down field compared to the axial proton and has a smaller *J* value. The structural assignment of VI was supported by the PMR signal for H-3 methine proton at δ 2.62-3.05 as a broad up-field multiplet. In our experiment the methyl ester was found to remain intact, showing mild reaction conditions.



I R=OH, R^1=H, R^2=COOH
II R=OH, R^1=H R^2=COOMe
III R=OAc, R^1=H, R^2=COOH
IV R, R^1 = = O R^2=COOMe
V R, R^1 = = NOH R^2=COOMe
VI $R=NH_2$, R^1=H, R^2=COOMe
VII R=OAc, R^1=H, $R^2=CONH_2$
VIII R=OAc, R^1=H, $R^2=CH_2NH_2$
IX R=OAc, R^1=H, $R^2=NH_2$

3β-Acetoxy-18-H-urs-12-en-28-methyl amine (VIII; m.p. 240°) was prepared by conversion of acetylursolic acid (III; m.p. 288-89°; lit.[5] m.p. 289-90°) into 3β-acetoxy-urs-12-en-28-carboxamide (VII; m.p. 305°) followed by LAH reduction of VII in ether. The products formed were characterized by their IR, PMR and mass spectra which also showed that LAH did not affect the acetoxy group during reduction of the amide group. Acetylursolic acid (III) underwent Curtius rearrangement in the presence of sodium azide and strong acidic condition to give 28-amino-3β-acetoxy-18β-H-urs-12-ene (IX; m.p. 210-11°) which was characterized by IR, PMR and mass spectral data.

Methyl ester of 3β-amino-18β-H-urs-12-en-28-oic acid (VI)

Sodium (2 g) was added portionwise to a warm solution of the oxime V (1 g) in 1-propanol (200 ml) at a rate which maintained the solution at gentle reflux. The mixture was then boiled for 2 hr, cooled and diluted with saturated aq. sodium chloride (200 ml). The aqueous layer was extracted with ether and the solvent removed from the combined organic extracts under reduced pressure. The residue was dissolved in ether

and the solution washed with brine till neutral, dried (Na_2SO_4) and solvent removed under reduced pressure to give a solid which on purification by column chromatography on silica gel afforded VI, m.p. 255-56 (yield, 0.6 g); IR (KBr): 3400 $(NH)_2$, 1715 (C = O), 1440, 1370; PMR (CCl_4): δ 5.25 (*t*, *J* 2.5 Hz, 1H, H-12), 3.55 (*s*, 3H, COOMe), 2.62-3.05 (br *m*, 3α-methine H); analysed for $C_{31}H_{51}O_2N$; M^+ 469.

Dry hydrogen chloride gas was bubbled through a cooled solution of VI (0.5 g) in methylene chloride-methanol (1:3 v/v, 100 ml) for several minutes, and solvent removed under reduced pressure to afford a cream-yellow solid which on recrystallization from methanol-ether furnished VI.HCl (0.45 g) as needles, m.p. 298-99°; IR (KBr): 3450, 1720 (C = O), 1600, 1510 (NH_3^+), 1450, 1370.

3β-Acetoxy-18β-H-urs-12-en-28-carboxamide (VII)

Freshly distilled thionyl chloride (2.5 ml) was added to a solution of III (2 g) in dry benzene, the mixture refluxed for 4 hr and excess thionyl chloride distilled off azeotropically. The acid chloride thus obtained in benzene was treated with excess of dry ammonia gas at 0° left overnight in a refrigerator, benzene removed and water added. The solid obtained was filtered, washed with water, dried and crystallized from methanol to give VII as a white solid, m.p. 305-6°; IR (KBr): 3470, 1725, 1670, 1450, 1360, 1240; PMR (CCl_4): δ 5.16 (*t*, *J* = 2.5 Hz, 1H, H-12), 4.35 (*t*, *J* = 3, 1H, H-3), 1.98 (*s*, 3H, $OCOCH_3$); analysed for $C_{32}H_{51}O_3N$; M^+ 497.

3β-Acetoxy-18-β-H-urs-12-en-28-methyl amine (VIII)

A solution of VII (0.5 g) in dry ether (100 ml) was added dropwise to a stirred suspension of LAH (0.3 g) in dry ether. The mixture was left at room temperature and ethanol added to it dropwise to destroy the excess hydride. After filtration, solvent was removed under reduced pressure and the residue crystallized from benzene to yield a white solid, m.p. 240-41°; IR (KBr): 3500, 1670, 1440, 1370; PMR (CCl_4): δ 5.3 (*t*, *J* = 2.5 Hz, 1H, H-12), 4.42 (*t*, *J* = 3, 1H, H-3), 3.76 (*m*, 2H, H-28), 1.92 (*s*, 3H, $-OCOCH_3$), analysed for $C_{32}H_{53}O_2N$; M^+ 483.

Hydrochloride: m.p. 272°; IR (KBr): 3420, 1720, 1670, 1510, (NH_3^+), 1440, 1370.

28-Amino-3β-acetoxy-18β-H-urs-12-ene (IX)

Sodium azide (150 mg) in small portions was added to a mixture of II (0.35 g), conc. H_2SO_4 (3.5 ml) and $CHCl_3$ (5 ml) with stirring at 50-55° during 45 min, heated for another 30 min at 50°, cooled, diluted with ice water (200 ml) and $CHCl_3$ layer separated. The aqueous acidic layer was made alkaline with liquor ammonia and repeatedly extracted with chloroform and dried (Na_2SO_4). Removal of chloroform gave a solid which was crystallized from benzene pet. ether giving the TLC-pure IX (50 mg), m.p. 210-11°; IR (KBr): 3450, 1720, 1640, 1450 and 1370; analysed for $C_{31}H_{51}O_2N$; M^+ 469.

Hydrochloride: m.p. >300°; IR (KBr): 3450 and 3200, 1720, 1690, 1660, 1510 (NH_3^+), 1450, 1360.

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Studies on Nitrosochlorination: Part III—Epithio Fatty Acids: A Route to the Synthesis of Thionitrites

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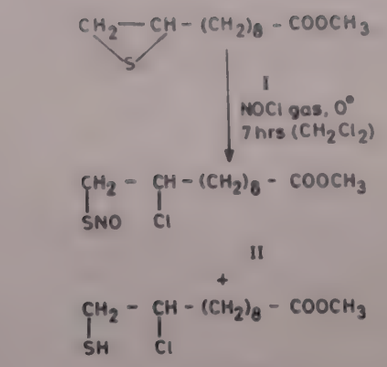
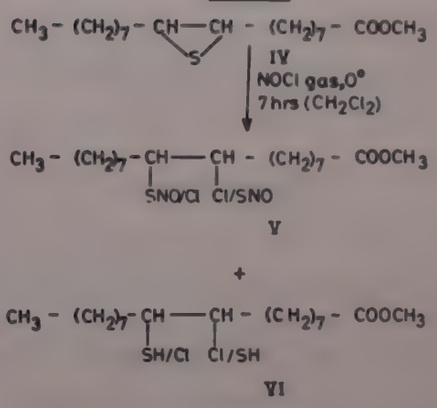
Epithio derivatives of the esters of undecenoic (I), oleic (IV) and vernolic (VII) acids have been subjected to nitrosochlorination with gaseous nitrosyl chloride. Compounds I and IV furnish their respective chlorothionitrites (II and V) and chlorothiols (III and VI), while compound VII gives the double bond addition products along with chlorothionitrites and chlorothiols (VIII, IX and X). The proposed structures for the products are based on elemental analyses and spectral data.

Although reports on the use of NOCl for nitrosochlorination of olefinic compounds are well documented[1], such a reaction remains relatively unexplored on fatty acids. Recently this reaction has been carried out in our laboratory on unsaturated fatty acids[2], β- and γ-hydroxy[3] and epoxy[4] fatty acids. Thionitrites (RSNO) are much less commonly encountered than their oxygen analogues, the nitrites. A number of aryl- and alkylthionitrites have been prepared from htiols and dinitrogen[5] tetroxide. Due to our interest in the synthesis of long-chain thionitrites and in continuation of our work on nitrosochlorination, we report herein the preparation of thionitrites from a variety of epithio fatty acid esters.

Nitrosochlorination of the epithio ester I gave two products (II and III) (Scheme 1). Product II (positive to Beilstein test) showed a characteristic IR band for thionitrito group (SNO) at 1530 cm^{-1} and multiplets at δ4.15 ($CH-Cl$) and 3.3-3.0 (CH_2-SNO), suggesting its structure as methyl 10-chloro-11-thionitritoundecanoate. The exclusive formation of 10-chloro-11-thionitrito isomer is in conformity with the reported ring opening reactions of terminal epithio compounds. Like nitrito derivatives[4], thionitrites are also very unstable and easily hydrolyzed to thiols. Product III which gave positive Beilstein test was characterized as methyl 10-chloro-11-mercaptoundecanoate, a hydrolyzed product of II. Its IR spectrum showed weak stretching bands at 2660 (SH) and 725 cm^{-1} (C−Cl) and PMR spectrum exhibited characteristic signals at δ4.3 (CH−Cl), 3.1 (CH_2−SH) and 1.5 (SH). The structure was further supported by its mass spectrum.



Scheme 1



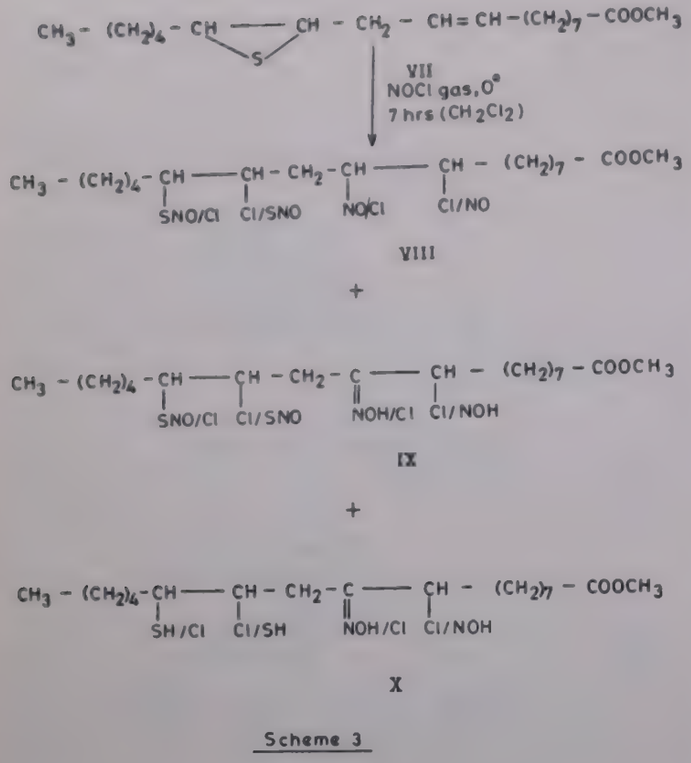
Scheme 2

Similar treatment of methyl 9,10-epithiooctadecanoate (IV) with NOCl gas yielded two products, V and VI (Scheme 2), which were characterized as methyl 9(10)-chloro-10(9)-thionitritooctadecanoate and methyl 9(10)-chloro-10(9)-mercaptooctadecanoate respectively by their IR and PMR data.

Similar treatment of methyl *cis*-12,13-epithio-*cis*-9-octadecenoate (VII) with nitrosyl chloride gas yielded three products, VIII, IX and X (Scheme 3). The product VIII was found to contain both thionitrito and nitroso groups and showed IR bands at 1550 (NO), 1535 (SNO) and 720 cm^{-1} (C−Cl). Its PMR spectrum showed a multiplet at δ4.2 (2×CH−Cl), 3.6-3.4 (CH−SNO) and 3.25 (−CH−NO). This product is formed by a simple addition of NOCl to the double bond and the cleavage of epithio ring.

Nitroso group, if attached to a carbon atom having a hydrogen, is known[3] to isomerize to oximino group. The product IX showed IR bands at 3450 and 1630 cm^{-1} suggesting the formation of isomerized oximino group. Besides these, thionitrito and C−Cl stretchings were also observed. On the basis of these and PMR spectral data (*vide infra*), the plausible structure of methyl 9(10),12(13)-dichloro-10(9)-oximino-13(12)-thionitritooctadecanoate was assigned to IX.

Product X was characterized as methyl 9(10), 12(13)-dichloro-10(9)-oximino-13(12)-mercaptooctadeca-



Scheme 3

noate. It is formed due to the hydrolysis of thionitrito group of IX to the mercapto group.

Pure samples of II, V, VIII and IX, on keeping at room temperature for more than 8 hr, were found to be contaminated with products III, VI, X and X respectively indicating the low stability of thionitrites[6,7].

Prolonged reaction period (7 hr) for nitrosochlorination of episulphides as compared with their epoxy counterparts[4] (30 min) can be justified on the basis of low reactivity of episulphides towards NOCl.

Thionitrites are now becoming increasingly useful as a source of thiyl radicals[8a] or as nitrosating agents[8b]. The present study of the reaction of NOCl with epithio fatty acids, apart from its inherent interest, shed new light on the use of nitrosyl chloride reactivity in the synthesis of thionitrites. The reaction is simple and gave thionitrites in high yields.

Experimental details have been given in earlier publications[3,4]. Epoxy esters of undecenoic, oleic and vernolic acids were treated with thiourea solution in water following the procedure of Kaufmann and coworker[9]. The crude epithio products thus obtained were purified by passing through a column of silica gel. All the three episulphides (I, IV, VII) gave positive sodium nitroprusside test for sulphur, and characteristic IR and PMR data.

Nitrosochlorination of methyl 10,11-*epithioundecanoate (I)*

NOCl gas[10] was passed slowly into a solution of I (1 g, 4.35 mmol) in methylene chloride (20 ml) at 0 (ice-salt bath) under stirring for about 7 hr and stirring continued further for 1 hr. The reaction mixture was kept overnight at 0°, excess of CH_2Cl_2 removed under reduced pressure, extracted with ether, and the ethereal extract washed with water, dried and evaporated to give a viscous syrup (~0.9 g) which showed one intense and one very faint spots on TLC.

The crude mixture was chromatographed over silica gel (20 g) column. TLC monitored eluates with pet. ether-ether (92:8, v/v) were combined to give II (65.5%) (Found: C, 48.7; H, 7.5; N, 4.7. $C_{12}H_{22}O_3NSCl$ requires C, 48.7; H, 7.5; N, 4.7%); IR: 1730 ($COOCH_3$), 1530 (SNO) and 730 (C–Cl) cm^{-1}; PMR: δ 4.15 (*m*, 1H, –CH–Cl), 3.7 (*s*, 3H, $COOCH_3$), 3.3-3.0 (*m*, 2H, $-CH_2-SNO$), 2.3 (*m*, 2H, $-CH_2COOCH_3$) and 1.35 (br *s*, 14H, chain-CH_2).

Subsequent elution with pet. ether-ether (90:10, v/v) yielded the product III (~30%) (Found: C, 54.0; H, 8.7. $C_{12}H_{23}O_2SCl$ requires C, 54.0; H, 8.7%); IR: 2660 w (SH), 1740 ($COOCH_3$), 725 (C–Cl) cm^{-1}; PMR: δ 4.3 (*m*, 1H, –CH–Cl), 3.1 (*m*, 2H, $-CH_2-SH$), 1.5 (1H, SH) and other usual fatty acids signals; MS: *m/z* 266/268 (M^+), 87 (base peak).

Nitrosochlorination of IV

Nitrosochlorination of IV (1 g, 3.040 mmol) was done under similar conditions. The crude product after usual work-up showed the presence of two components on TLC. These products were separated by column chromatography over silica gel (25 g). First fraction, eluted with pet. ether-ether (96:4, v/v), gave V (~62.0%) (Found: C, 57.9; H, 9.2; N, 3.5. $C_{19}H_{36}O_3NSCl$ requires C, 57.9; H, 9.2; N, 3.6%); IR: 1740 ($COOCH_3$), 1535 (SNO) and 730 (C–Cl) cm^{-1}; PMR: δ 4.4 (*m*, 1H, –CH–Cl), 3.6 (*s*, 3H, $-COOCH_3$), 3.3 (*m*, 1H, –CH–SNO), 2.2 (*m*, 2H, $-CH_2COOCH_3$), 1.35 (br *s*, 26H, chain-CH_2) and 0.9 (*t* like, 3H, terminal CH_3).

Subsequent elution with pet. ether-ether (92:8; v/v) yielded the product VI (~24.0%) (Found: C, 62.5; H, 10.2. $C_{19}H_{37}O_2SCl$ requires C, 62.5; H, 10.2%); IR: 2660 w (SH), 1735 ($COOCH_3$), 725 (C–Cl) cm^{-1}; PMR: δ 4.4 (*m*, 1H, –CH–Cl), 3.6 (*s*, 3H, $-COOCH_3$), 3.2 (*m*, 1H, $-CH-SH$), 2.3 (*m*, 2H, $-CH_2COOCH_3$), 1.5 (*s*, 1H, SH), 1.35 (br *s*, 26H, chain-CH_2) and 0.9 (*t* like, 3H, terminal CH_3).

Nitrosochlorination of VII

Nitrosochlorination of VII (2 g, 6.120 mmol) was also carried out under similar conditions. The crude product obtained after usual work-up showed the presence of three components. It was chromatographed over silica gel (50 g) column. Elution with pet. ether-ether (97:3, v/v) yielded the product VIII

(~36.5%) (Found: C, 49.9; H, 7.4; N, 6.1. $C_{19}H_{34}O_4N_2SCl_2$ requires C, 49.9; H, 7.5; N, 6.1%); IR: 1740 ($COOCH_3$), 1550 (NO), 1535 (SNO) and 720 (C–Cl) cm^{-1}; PMR: δ 4.2 (*m*, 2H, 2 × –CH–Cl), 3.6 (*s*, 3H, $-COOCH_3$), 3.6-3.4 (*m*, 1H, –CH–SNO, a part of multiplet merged with ester proton), 3.25 (*m*, 1H, –CH–NO), 2.3 (*m*, 2H, $-CH_2-COOCH_3$), 1.35 (br *s*, 22H, chain-CH_2) and 0.9 (*t* like, 3H, terminal CH_3).

Subsequent elution with pet. ether-ether (92:8, v/v) yielded the product IX (~22.5%) (Found: C, 49.9; H, 7.5; N, 6.1. $C_{19}H_{34}O_4N_2SCl_2$ requires C, 49.9; H, 7.5; N, 6.1%); IR: 3450 (NOH), 1740 ($COOCH_3$), 1630 (C=N str.), 1540 (SNO) and 720 (C–Cl) cm^{-1}; PMR: δ 7.2 (*s*, 1H, =NOH, exchangeable with D_2O), 4.55 (*m*, 1H, –CH–Cl, adjacent to oximino group), 4.22 (*m*, 1H, –CH–Cl, adjacent to thionitrito function), 3.6-3.4 (*m*, 1H, CH–SNO) and other usual fatty acid signals.

Further elution with pet. ether-ether (88:12, v/v) yielded the product X (~21.0%) (Found: C, 53.2; H, 8.2; N, 3.3; $C_{19}H_{35}O_3NSCl_2$ requires C, 53.3; H, 8.2; N, 3.3%); IR: 3400 (NOH), 2660w (SH), 1740 ($COOCH_3$), 1630 (C=N str.) and 720 (C–Cl) cm^{-1}; PMR: δ 7.2 (*s*, 1H, =NOH, exchangeable with D_2O), 4.8 (*m*, 1H, –CH–Cl, adjacent to oximino group), 4.2 (*m*, 1H, –CH–Cl, adjacent to mercapto group), 3.2 (*m*, 1H, –C*H*–SH) and 1.5 (1H, SH) and other usual fatty acid signals.

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A Novel Photo-oxygenation Reaction of Diosgenin

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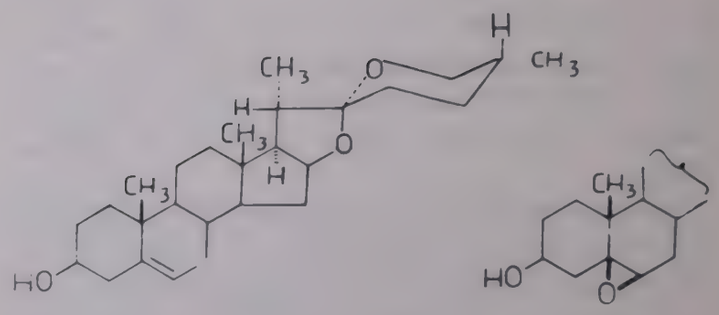
Prolonged irradiation by ultraviolet light of an acetone solution of diosgenin furnishes (25 *R*)-spirostan-5β,6β-epoxy-3β-ol in about 15% yield.

In a programme to study the photochemistry of the insect hormone, ecdysone[1], we have presently studied the effect of UV irradiation on diosgenin as a model compound.

An acetone solution of diosgenin on irradiation for 48 hr, afforded, after usual work-up, a white crystalline photoproduct (I), m.p. 206°, which exhibited in its IR spectrum, in KBr, bands at 1250, 1180, 1165, 1085, 1070, 1060, 1045, 1020, 970, 910 and 870 cm^{-1} in the finger-print region, closely resembling those of the starting diosgenin. This indicated that the basic molecular framework of diosgenin was largely retained in I and no deep seated photo-rearrangement had occurred in its formation. This view was further supported by the mass fragmentation data of I. Thus the appearance of peaks at *m/z* 139 (base peak) and 115 indicated the presence of spiroketal system in the molecule[2].

The photoproduct exhibited the molecular ion (M^+) at *m/z* 430, which was 16 mass units higher than that of the diosgenin. It appeared that one oxygen atom (presumably derived from atmospheric air) had added onto diosgenin, during the photolytic process. The oxygen could either be inserted, as a hydroxylic function or added across the C_5-C_6 olefinic double bond of the diosgenin molecule to give an epoxide. The latter alternative was favoured, since the IR bands of diosgenin[3a] located at 1670, 815 and 805 cm^{-1} (tri-substituted double bond) were conspicuously absent in the IR spectrum of I. The appearance of bands at 950, 925, 830, 780 and 765 cm^{-1} in I. provided support to the epoxide formation[3b,4]. The PMR data were also in accord with this conclusion[5]. Thus, the PMR spectrum of I in $CHCl_3$ did not exhibit any signal around δ 5.35 due to vinylic proton. However, a split signal centered at δ 3.05[7], due to a proton attached to C-6 of oxirane ring was observed. The position of this signal revealed β-orientation of the oxirane ring in I. The corresponding α-derivative would show a signal



(Diosgenin) (I)

centered around δ 2.82[6]. Examination of the Dreiding model shows that A/B ring junction is *cis*. Based on the above considerations the structure of I can be represented as 5β,6β-epoxydiosgenin.

Diosgenin was isolated[7] from the rhizomes of *Dioscorea deltoidea* Wall. and purified by preliminary chromatography, followed by acetylation (Py-Ac_2O), alkaline hydrolysis and careful rechromatography over silica gel. The compound, m.p. 204-5° was found to be homogenous by HPLC.

Diosgenin (450 mg) was dissolved in acetone (500 ml) and irradiated in a photochemical reactor (equipped with 2537 Å light source) for 48 hr. Work-up furnished a solid, which was chromatographed on silica gel. Petroleum ether-ethyl acetate (7:3) eluted the 5β,6β-epoxide (68 mg, ~15%), m.p. 206°; R_f(I), 0.22; R_f (diosgenin), 0.56 (solvent system: as above) (Found: C, 75.0; H, 9.8. $C_{27}H_{42}O_4$ requires C, 75.3; H, 9.8%); PMR ($CHCl_3$): δ 4.35 (*m*, 1H), 3.05 (*m*, 1H), 1.00 (*s*, 3H); MS (70 eV): *m/z* (rel. intensity, %) 430 (M^+, 5.5), 371 (4.2), 361 (6.7), 358 (12.1), 316 (8.5), 298 (9.6), 287 (9.7), 269 (6.4), 251 (4.7), 177 (18.5), 141 (12.5), 139 (100.0) and 115 (10.0).

We wish to thank Dr K P Madhusudanan and Mr R K Singh of CDRI, Lucknow, for the mass spectrum of I.

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Ceric Ammonium Nitrate Oxidation of Esters

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Ceric ammonium nitrate oxidation of esters affords the corresponding acids.

In our on-going research programme on the ceric ammonium nitrate (CAN) oxidations[1-3], we now wish to report the oxidation of esters by CAN to the corresponding acids. There are several reports[4-10] in the literature describing the oxidation of esters by other oxidants.

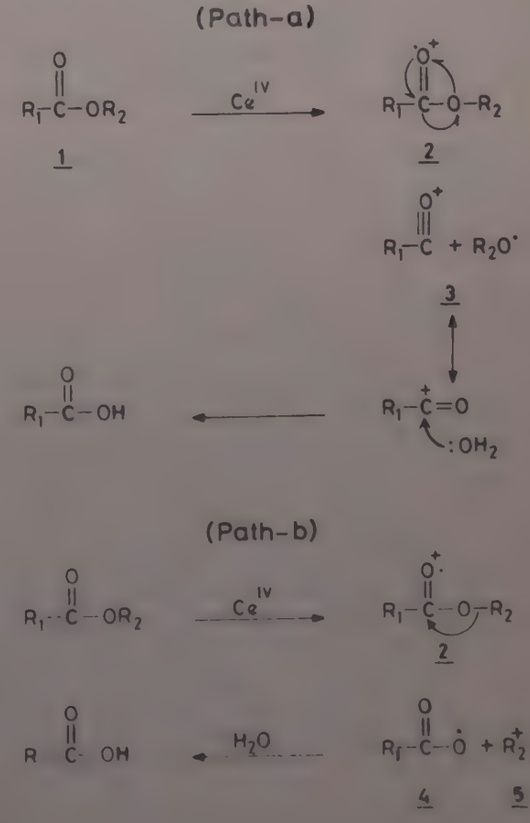
In a typical procedure, to a stirred solution of ester (1 mmol) in aq acetonitrile (1:4, 5 ml) was added a solution of CAN (4 mmol) and the resulting solution refluxed for 5-6 hr at 80°. It was allowed to cool to room temperature, diluted with water (10 ml) and extracted with ether (3 × 5 ml) and the ethereal layer extracted with sodium bicarbonate solution (5%). The aqueous alkaline layer was acidified (dil HCl), extracted with ether (3 × 5 ml). The organic extract dried (Na_2SO_4), concentrated and the solid acid obtained recrystallized and fully characterized by direct comparison of their physical and spectral data with those of the authentic samples reported in literature. The acids thus prepared are listed in Table 1.

The reaction is believed to proceed via an electron transfer from oxygen to cerium producing a radical cation (**2**) (path-a, path-b) (see Scheme 1). It is reasonable to visualize fragmentation of **2** to acyl cation (**3**), which can then be converted into a carboxylic acid in aqueous medium. On the otherhand **2**, can undergo fragmentation to give the carbonium ion (**5**) and carboxylic radical (**4**). The path-b would be favoured for the cleavage of allylic and benzylic esters because of the increased stability of the cation.

The intermediacy of the acyl cation in the case of oxidative cleavage of methyl benzoate is established by carrying out the reaction in the presence of *t*-butanol instead of water. The product of the reaction is found to be *t*-butyl ester of benzoic acid, instead of benzoic acid. Reaction of *p*-nitrobenzyl benzoate with CAN in aq acetonitrile gives lower yield of the benzoic acid. The same reaction when conducted in *t*-butanol/acetonitrile results in the formation of *t*-butyl ester of the benzoic acid. These observations suggest that in the case of benzylic esters the mode of oxidative

Table 1—Ceric Ammonium Nitrate Oxidation of Esters (R_1-$COOR_2$)

Sl No.	R_1	R_2	Acid (R_2 = H) m.p.(°C)	Yield (%)
1	C_6H_5	CH_3	122-23	56
2	C_6H_5	C_2H_5	122-23	59
3	C_6H_5	*n*-C_3H_7	120-22	61
4	*p*-ClC_6H_4	C_2H_5	238-40	58
5	*m*-ClC_6H_4	C_2H_5	154-56	58
6	*p*-$NO_2C_6H_4$	C_2H_5	239-40	62
7	*p*-BrC_6H_4	C_2H_5	251-53	65
8	C_6H_5	$-CH_2CH=CH_2$	121-23	78
9	*p*-ClC_6H_4	$-CH_2CH=CH_2$	239-40	74
10	*m*-ClC_6H_4	$-CH_2CH=CH_2$	155-56	70
11	*p*-$NO_2C_6H_4$	$-CH_2CH=CH_2$	238-40	70
12	*p*-$CH_3C_6H_4$	$-CH_2CH=CH_2$	179-81	69
13	*p*-$OCH_3C_6H_4$	$-CH_2CH=CH_2$	181-85	85
14	C_6H_5	$-CH_2C_6H_5$	121-23	64
15	*p*-ClC_6H_4	$-CH_2C_6H_5$	239-40	65
16	*p*-$CH_3C_6H_4$	$-CH_2C_6H_5$	181-82	70
17	$C_6H_5CH_2$	C_2H_5	76-77	68
18	$C_6H_5CH_2$	*n*-C_3H_7	75-77	65



cleavage is via the benzylic cation (5) (path-b), whereas in the case of normal esters the cleavage probably takes place via the acyl cation (3) (path-a).

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Photolysis of N-Nitrosodiphenylamines & N-Nitrosocarbazole†

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N-Nitrosodiphenylamine, N-nitroso-2-nitrodiphenylamine and N-nitrosocarbazole on irradiation in benzene give products resulting from nitroso group migration.

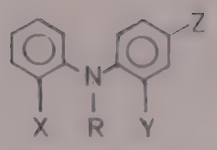
Formationof 2- and4-nitrodiphenylamines alongwith diphenylamine, 2- and 4-nitrosodiphenylamines and a trace of carbazole has been reported by Rikuhei[1] from the irradiation of N-nitrosodiphenylamine in ethanol for about 3 hr in a degassed solution. However, Crumrine *et al.*[2] isolated diphenylamine and carbazole from the same starting material in the same solvent. The latter workers[2] attributed the formation of diphenylamine to easy availability of proton in solution. It was further explained that prolonged irradiation of the resultant diphenylamine leads to the formation of carbazole.

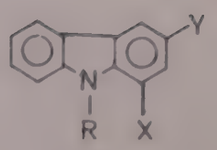
In view of the above conflicting results it was thought worthwhile to reinvestigate this reaction in benzene solution. In the present study substituted N-nitrosodiphenylamines and N-nitrosocarbazole have been irradiated in benzene under nitrogen atmosphere.

N-Nitrosodiphenylamine (I)[3] was irradiated for 30 hr in benzene at room temperature when 2-nitro-(II)[4] and 4-nitro-(III)[5]-diphenylamines were obtained in 2.2 and 5.3% yields respectively. The unreacted I (77.5%) and diphenylamine (IV; 6.2%) were also obtained. However, the formation of carbazole derivatives could not be detected. A polymer (1.9%) and an unidentified red compound (1.1%) were obtained which could not be identified.

Similarly N-nitroso-2-nitrodiphenylamine (V)[3] on irradiation under similar conditions, gave 2,2′-dinitro-(VI)[6]- and 2,4′-dinitro-(VII)[6]-diphenylamines in 20.1 and 48.2% yields, respectively besides 2-nitrodiphenylamine (VIII[4]; 16.2%) and an intractable tar (5.7%).

Likewise N-nitrosocarbazole (IX)[3] on irradiation in benzene in a pyrex reactor afforded 1-nitro-(X)[7]- and 3-nitro-(XI)[8]-carbazoles in 3.7 and 9.7% yields, respectively in addition to carbazole XII (7.04%), the starting material (IX; 76%) and an unidentified product (2%).





I. X = Y = Z = H, R = NO

II. X = Z = R = H, Y = NO_2

III. X = Y = R = H, Z = NO_2

IV. X = Y = R = Z = H

V. X = NO_2, Y = Z = H, R = NO

VI. X = Y = NO_2, Z = R = H

VII. X = Z = NO_2, Y = R = H

VIII. X = NO_2, Y = R = Z = H

IX. X = Y = H, R = NO

X. X = NO_2, Y = R = H

XI. X = R = H; Y = NO_2

XII. X = Y = R = H

In order to confirm further whether the rearrangement is intramolecular or intermolecular, an equimolecular mixture of N-nitrosodiphenylamine and anisole was irradiated. However, not even a trace of nitroso- or nitro-anisole was obtained. The products were identical with the photolysis products of I.

An equimolecular mixture of I and 4,4′-dimethyldiphenylamine was also irradiated under similar conditions. Again not even a trace of cross-over products could be obtained.

The structure of the photolysis products were established by elemental analysis, IR, PMR and mass spectral data as well as by comparison with authentic samples wherever possible.

According to Crumrine *et al.*[2] the reaction proceeds through the homolytic fission of the N−N bond of N−N=O followed by free-radical attack at the carbon atom of phenyl ring. However, failure of attack by the nitroso radical on the electron rich species like anisole and 4,4′-dimethyldiphenylamine fails to corroborate the theory of homolytic fission of N−N bond although the formation of diphenylamine can only be explained by the homolytic fission of the N−N bond. Alternatively, it may be possible that both the mechanisms concerted as well as free-radical may be operating simultaneously. Failure of cross-over experiments may be due to the fact that the energy of activation for the interaction of diphenylamine radical with nitroso radical, is more than that for the interaction of diphenylamine radical with nitroso radical, i.e. E_a' (DPH + NO) > E_a(DP + NO). Moreover in degassed solutions the nitroso radical gets out of the reaction mixture as nitric oxide gas[9].

†Part II of the series "Organic Photochemistry

Melting points are uncorrected. IR (KBr) spectra were run on a Beckmann IR-20 spectrophotometer (ν_{max} in cm^{-1}) and PMR spectra on a Perkin-Elmer R-32 instrument (chemical shift in δppm).

N-Nitrosodiphenylamine (I; m.p. 65-66°), N-nitroso-2-nitrodiphenylamine (V; m.p. 99-100°) and N-nitrosocarbazole (IX; m.p. 80-81°) were prepared as described in literature[3].

Photolysis: General Procedure

To a two-piece pyrex photoreactor was added appropriate N-nitroso compound (0.02 mol) in benzene (200 ml) and subjected to irradiation by medium pressure 125 W mercury vapour lamp under nitrogen atmosphere for 20-30 hr. The photolysate was stripped of the solvent and fed onto a column of silica gel and eluted gradually with solvents of increasing polarity. Fractions of 25 ml size were collected, tested on TLC for purity and those having similar R_f were combined and their solvents removed to obtain TLC pure products. Their structures were elucidated by their PMR, IR and mass spectral data as given below:

2-Nitrodiphenylamine (*II*)—Yield 2.2%, m.p. 75-76° (lit.[4], m.p. 75.5°); $R_f = 0.72$; PMR ($CDCl_3$): 9.46 (1H, *bs*, NH), 8.19 (1H, *dd*, H-3), 7.48 (1H, *d*, H-5), 7.42-7.10 (5H, m, H-4, H-6, H-3′, H-4′ and H-5′), 6.75 (2H, *t*, H-2′ and H-6′); $J_{3,4} = 9$ Hz, $J_{3,5} = 2.5$ Hz, $J_{2',3'} = J_{5',6'} = 9$ Hz, $J_{2',4'} = J_{2',6'} = J_{3',5'} = 2.5$ Hz.

4-Nitrodiphenylamine (*III*)—Yield 5.3%, m.p. 132-33° (lit.[5], m.p. 133.5-134.5°); $R_f = 0.38$; IR: 3350 (NH), 1500 and 1320 (NO_2); PMR ($CDCl_3$): 8.0 (2H, *d*, H-3 and H-5), 7.40-7.15 (3H, *m*, H-3′, H-4′ and H-5′), 7.12 (2H, *d*, H-2 and H-6), 6.85 (2H, *dd*, H-2′ and H-6′); $J_{2,3} = J_{2',3'} = 9$ Hz, $J_{2',4'} = J_{4',6'} = 3$ Hz; MS: *m/z* 214 (M^+), 184 (M − NO), 168 (M − NO_2), 167 (M − HNO_2).

2,2′-Dinitrodiphenylamine (*VI*)—Yield 20.1%, m.p. 165-66° (lit.[6], m.p. 166-67°); $R_f = 0.53$; IR: 3300 (NH), 1610 (NH bending), 1520, 1330 (NO_2); PMR ($CDCl_3$): 8.05 (2H, *dd*, H-3 and H-3′), 7.50-7.40 (4H, m, H-4, H-5, H-4′ and H-5′), 7.10 (2H, *dd*, H-6 and H-6′); MS: *m/z* 259 (M^+), 213 (M − NO_2), 212 (M − HNO_2).

2,4′-Dinitrodiphenylamine (*VII*)—Yield 48.2%, m.p. 218-19° (lit.[6], m.p. 219°); $R_f = 0.50$; IR: 3320 (NH), 1620 (NH bending), 1500 and 1330 (NO_2); PMR (DMSO-d_6): 9.40 (1H, *bs*, NH), 8.14 (2H, *d*, H-3 and H-5), 8.10 (1H, *dd*, H-3), 7.80-7.50 (2H, *m*, H-4 and H-5), 7.30 (1H, *dd*, H-6), 7.24 (2H, *d*, H-2′ and H-6′); $J_{3,5} = J_{5',6'} = J_{5,6} = J_{3,4} = J_{4,5} = 9$ Hz, $J_{3,5} = J_{4,6} = 3$ Hz; MS: *m/z* 259 (M^+), 258 (M − H), 212 (M − HNO_2), 211 (M − H_2NO_2).

1-Nitrocarbazole (*X*)—Yield 3.69%; m.p. 186-87° (lit.[7], m.p. 187°); $R_f = 0.41$; IR: 3320 (NH), 1610 (NH bending), 1520 and 1320 (NO_2); PMR ($CDCl_3$): 8.35 (1H, *dd*, H-4), 8.25 (1H, *dd*, H-5), 8.10 (1H, *dd*, H-2), 7.55 (1H, *dd*, H-7), 7.40 (1H, *q*, H-3), 7.25 (2H, *dd*, H-3 and H-6), $J_{2,3} = J_{3,4} = J_{7,8} = J_{5,6} = 9.5$ Hz, $J_{2,4} = 2.5$ Hz.

3-Nitrocarbazole (*XI*)—Yield 9.7%, m.p. 213-14° (lit.[8], m.p. 214°); $R_f = 0.33$; IR: 3300 (NH), 1615 (NH bending), 1500 and 1320 (NO_2); PMR ($CDCl_3$): 8.80 (1H, *d*, H-4), 8.30 (1H, *d*, H-5), 8.12 (1H, *d*, H-2), 7.98 (1H, *d*, H-1), 7.45-7.30 (2H, *m*, H-7 and H-8) and 7.10 (1H, *q*, H-6); MS: *m/z* 212 (M^+), 166 (M − NO_2), 165 (M − HNO_2).

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Lead Tetraacetate Oxidation of Chalcone Oximes

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Chalcone oximes (Ia-e) are oxidised by lead tetraacetate in dry benzene to afford the parent ketones (IIa-e) and the corresponding isoxazoles (IIIa-e).

Various aspects of lead tetraacetate (LTA) oxidation of aldoximes and ketoximes have been studied by different workers[1-3]. Looking to the interesting results obtained, it was considered worthwhile to study oxidation of chalcone oximes with LTA in dry benzene. In the present note, we report the formation of parent ketones (IIa-e) in addition to isoxazoles (IIIa-e) in encouraging yields.

Chalcone oximes (Ia-e) were prepared by the action of hydroxyl amine hydrochloride on chalcones (IIa-e). The identity of chalcones (IIa-e) obtained by the LTA oxidation of Ia-e was confirmed by direct comparison (m.m.p. and co-IR) with authentic samples. The structures of the isoxazoles (IIIa-e) were established by elemental analyses IR and PMR data and their synthesis from chalcone dibromide following the literature procedure[4]. In the PMR spectra of compounds (IIIa-e) the ethylenic protons appeared in the region δ 6.55-6.80.

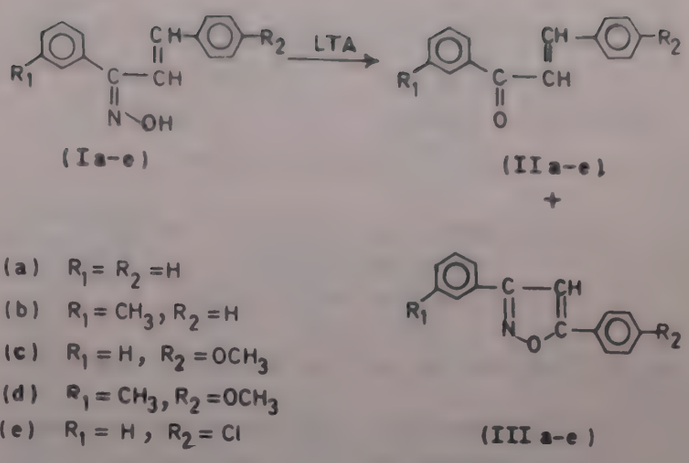

Table 1—Characterisation Data of Oxidation Products (IIa-e and IIIa-e) of Chalcone Oximes (Ia-e)

Chalcone oxime (I)	Mol. formula	m.p. °C	Oxidation products	m.p. °C	Yield %
a	$C_{15}H_{13}ON$	140	IIa	56	29.4
			IIIa	140	28.5
b	$C_{16}H_{15}ON$	132	IIb	78	26.42
			IIIb	128	27.0
c	$C_{16}H_{15}O_2N$	100	IIc	75	31.3
			IIIc	125	25.8
d	$C_{17}H_{17}O_2N$	150	IId	94	33.6
			IIId	130	24.0
e	$C_{15}H_{12}ONCl$	153	IIe	103	30.5
			IIIe	178	28.1

All the isoxazoles gave satisfactory C, H and N analyses.

Oxidation of chalcone oximes: General procedure

A mixture of chalcone oxime (1 mol) and lead tetraacetate (1.2 mol) in dry benzene was refluxed for 4 hr and filtered. Usual work-up followed by fractional crystallisation afforded the products, which are listed in Table 1.

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Monoamine Oxidase & Succinate Dehydrogenase Inhibitory & Anticonvulsant Activities of Some 3-(N-Arylcarboxamidomethyl)-4-quinazolones

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3-(N-Arylcarboxamidomethyl)-4-quinazolones (IIIa-k), prepared from N-aryl-2-chloroacetamides (IIa-k) and 4-quinazolones (I), possess ALD_{50} values from 500-1000 mg/kg and found to inhibit rat brain monoamine oxidase (MAO) (30-65%) and succinate dehydrogenase (SDH) (10-80%) *in vitro* at a concentration of 5×10^{-4} *M* and provide 30-50% protection against pentylenetetrazole-induced convulsions in mice.

Quinazolone derivatives show a variety of biological activities like hypnotic, anticonvulsant, monoamine oxidase[1-4] (MAO) and succinate dehydrogenase inhibiting effects[5]. Amides such as 2-phenyl-2-hydroxypropionamide[6] and N-benzyl-β-chloropropionamide[7] and acetamide derivatives[8] possess anticonvulsant activity. In view of the above findings, we have synthesised some quinazolones (IIIa-k) incorporating N-arylcarboxamidomethyl group at position-3 and studied their MAO and succinate dehydrogenase (SDH) inhibitory and anticonvulsant activities.

The desired compounds 3-(N-arylcarboxamidomethyl)-4-quinazolones (IIIa-k; Table 1) were synthesised according to the method outlined in Scheme 1. These compounds were found to inhibit MAO to the extent of 30-65% at 5×10^{-4} *M* concentration while the reference compound pargyline caused 70% inhibition at 1×10^{-4} *M* concentration. Regarding substituent effect of phenyl ring, 4-nitro and 4-chloro compounds (IIIg and IIIi) were most effective (65%) and 2-chloro-5-nitro derivative (IIIg) was least active (30%). The 2- and 3-nitroderivatives (IIIe, f) produced 50 and 55% inhibition, respectively while 2-, 3- and 4-methoxy compounds were less effective compared to the nitro derivatives.

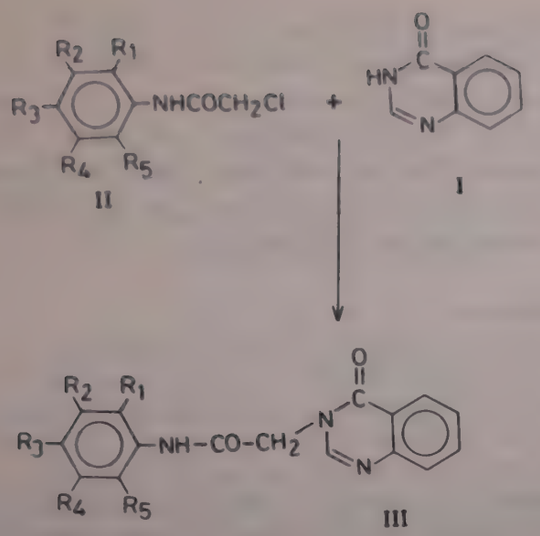
The 3-substituted quinazolones (IIIa-k) were also found to inhibit the activity of SDH at a final concentration of 5×10^{-4} *M* as compared with maleic acid (60%) at 1×10^{-4} *M* concentration. The 4-chloro

Table 1—Physical and Analytical Data of 2-Chloroacetamides (IIa-k) and 3-(N-Arylcarboxamidomethyl)-4-quinazolones (IIIa-k)

Compd	R_1	R_2	R_3	R_4	R_5	m.p.* °C	Yield (%)	Mol. formula†
IIa	H	H	H	H	H	132	60	C_8H_8NOCl
IIb	OCH_3	H	H	H	H	150	70	$C_9H_{10}NO_2Cl$
IIc	H	H	OCH_3	H	H	160	75	$C_9H_{10}NO_2Cl$
IId	H	OCH_3	H	H	H	156	72	$C_9H_{10}NO_2Cl$
IIe	NO_2	H	H	H	H	170	55	$C_8H_7N_2O_3Cl$
IIf	H	NO_2	H	H	H	156	58	$C_8H_7N_2O_3Cl$
IIg	H	H	NO_2	H	H	180	50	$C_8H_7N_2O_3Cl$
IIh	CH_3	CH_3	H	H	H	118	60	$C_{10}H_{12}NOCl$
IIi	CH_3	H	CH_3	H	CH_3	128	70	$C_{11}H_{14}NOCl$
IIj	H	H	Cl	H	H	140	65	$C_8H_7NOCl_2$
IIk	Cl	H	H	NO_2	H	125	62	$C_8H_6N_2O_3Cl_2$
IIIa	H	H	H	H	H	120	70	$C_{16}H_{13}N_3O_2$
IIIb	OCH_3	H	H	H	H	160	60	$C_{17}H_{15}N_3O_3$
IIIc	H	H	OCH_3	H	H	102	65	$C_{17}H_{15}N_3O_3$
IIId	H	OCH_3	H	H	H	105	75	$C_{17}H_{15}N_3O_3$
IIIe	NO_2	H	H	H	H	180	70	$C_{16}H_{12}N_4O_4$
IIIf	H	NO_2	H	H	H	83	60	$C_{16}H_{12}N_4O_4$
IIIg	H	H	NO_2	H	H	132	65	$C_{16}H_{12}N_4O_4$
IIIh	CH_3	CH_3	H	H	H	146	68	$C_{18}H_{17}N_3O_2$
IIIi	CH_3	H	CH_3	H	CH_3	180	65	$C_{19}H_{19}N_3O_2$
IIIj	H	H	Cl	H	H	152	70	$C_{16}H_{12}N_3O_2Cl$
IIIk	Cl	H	H	NO_2	H	170	55	$C_{16}H_{11}N_4O_4Cl$

*Compounds IIIa-k were recrystallised from aq. ethanol.

†Satisfactory elemental analyses were obtained for all the compounds.



SCHEME 1

compound (IIIj) was most effective (80% inhibition) while IIIf was least active (10% inhibition). Among the methoxy derivatives, 4-methoxy analogue was better than 2- and 3-methoxy analogues. When two methyl groups were present at 2- and 3-positions as in compound IIIh, the inhibition was found to be higher (60%) but the introduction of a third methyl group as in IIIi, caused a sudden decrease in the activity.

The compounds of the type III provided 20-50% protection against phenylenetetrazol-induced convulsions in mice at 100 mg/kg p.o. dose level compared to 100% activity of phenobarbitone (a reference drug) at 50 mg/kg p.o. The most active was 2-methoxy compound (IIIb; 50% protection) while the least active was 4-nitro derivative (IIIg; 20% protection). In these studies, higher mortality was observed with compounds IIIc, e, i, k, which were found to possess 30-40% anticonvulsant activity during 24 hr in pentylenetetrazol-treated animals, whereas compounds IIIb and IIId which exhibited a greater degree of protection elicited a lower pentylenetetrazol-induced mortality during 24 hr. In general, compounds III were found to possess low toxicity except IIIb, g, h, i (Table 2). The compounds containing NO_2 and Cl groups on the phenyl moiety exhibited better MAO inhibitory properties as compared to the compounds having methoxy group or unsubstituted phenyl ring. However, compounds possessing NO_2 group were found to be poor inhibitors of SDH activity. Compounds having methoxy or methyl group on the phenyl ring produced better SDH inhibitory activity. The above studies could not establish a definite correlation between enzyme inhibition and anticonvulsant activity of III.

Melting points are uncorrected and were taken in a sulphuric acid-bath. IR spectra were recorded in KBr (ν_{max} in cm^{-1}) on a Perkin-Elmer 377 spectrophotometer.

Table 2—MAO and SDH Inhibitory Activities and Anticonvulsant Activity of 3-(N-Arylcarboxamidomethyl)-4-quinazolones (IIIa-k)

Compd[a]	MAO inhibition[b] (%)	SDH inhibition[b] (%)	Anticonvulsant activity[c]		
			Protection against pentylenetetrazole (%)	Mortality (%)[d]	ALD_{50} (mg/kg p.o.)
Paragyline	70	—	—	—	—
Maleic acid	—	60	—	—	—
Phenobarbitone[e]	—	—	100	nil	—
IIIa	50	—	30	40	>1000
IIIb	50	40	50	40	500
IIIc	45	50	30	60	>1000
IIId	40	30	45	40	>1000
IIIe	50	20	40	60	>1000
IIIf	55	10	40	20	>1000
IIIg	65	30	20	20	500
IIIh	50	60	30	40	500
IIIi	40	30	40	60	500
IIIj	60	80	20	30	>1000
IIIk	30	20	40	60	>1000

[a]For compounds III the values of R_1 to R_5 are given in Table 1.
[b]Compounds were dissolved in propylene glycol; MAO and SDH inhibitory activities were observed at 5×10^{-4} *M* and 5×10^{-4} *M* concentrations, respectively.
[c]Compounds were administered at a dose of 100 mg/kg p.o.
[d]Mortality after 24 hr in each group of pentylenetetrazol-treated animals.
[e]Standard drug phenobarbitone at a dose of 50 mg/kg p.o., 4 hr before the administration of pentylenetetrazol (80 mg/kg s.c.).

4-Quinazolone (*I*)

It was obtained by the reported method[10] using anthranilic acid and formamide.

N-Aryl-2-chloroacetamides (*II*; *Table* 1)

A mixture of arylamine (0.01 mol) and chloroacetyl chloride (0.01 mol) in dry benzene was refluxed for 4-5 hr on a steam-bath and cooled. The solid separated was filtered, washed with water, dried and crystallised from a suitable solvent. IIf—IR: 3240 (NH), 1640 (CONH), 1340 ($C-NO_2$).

3-(N-Arylcarboxamidomethyl)-4-quinazolones (*III*; *Table* 1)

These were obtained by refluxing equimolar mixture of I and II in pyridine (15 ml) for 2 hr. Excess of pyridine was distilled off, the residue poured over crushed ice with constant stirring, filtered and the product washed with cold water and dried. It was

crystallised from acetone. IIIf—IR: 3320 (NH), 1690 (C=O of quinazolone ring), 1349 ($C-NO_2$).

Biological studies

Adult albino mice weighing approximately 100-150 g were killed by decapitation. Brains were quickly removed, cleaned of adhering tissues and blood, and kept in ice-bath till homogenisation, which was carried out in 0.25 *M* sucrose using Potter Elvehjem homogeniser consisting of glass tube and teflon pestle under cold conditions. Monoamine oxidase and succinate dehydrogenase inhibitory activities were determined using this preparation as a source of enzyme.

Monoamine oxidase inhibitory activity

It was determined by the method of Tabor *et al.*[11] using benzylamine as a substrate. The benzaldehyde formed during oxidative deamination of benzylamine was estimated spectrophotometrically on a Hitachi Perkin-Elmer spectrophotometer at 250 nm.

Succinate dehydrogenase inhibitory activity

It was determined spectrophotometrically using sodium succinate as substrate following the method of Slater and Bonner[12].

Anticonvulsant activity

It was determined against pentylenetetrazole-induced seizure in albino mice of either sex following the method of Swinyard *et al.*[13]. The ALD_{50} values were obtained by the method of Smith[14].

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Synthesis of Some New Substituted β-(2-Naphthoxy)propioanilides as Potential Anthelmintic Agents

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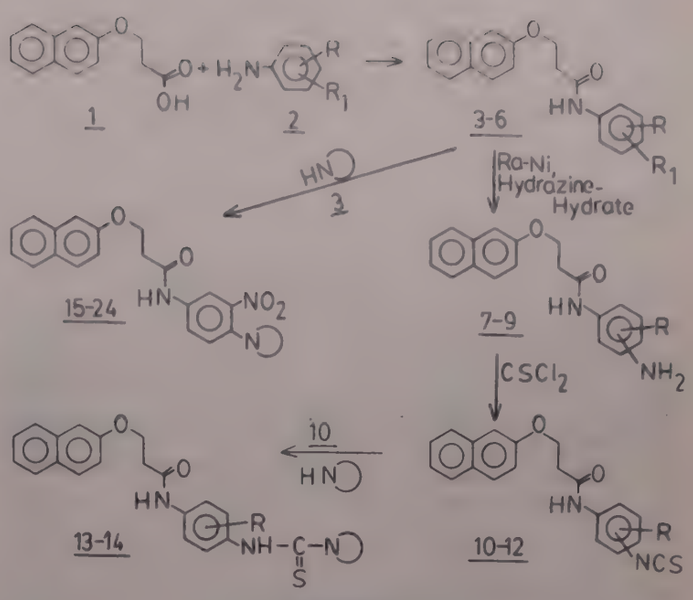
Various substituted β-(2-naphthoxy)propioanilides have been synthesised by the condensation of β-(2-naphthoxy) propionic acid with appropriate amines. Their *in vivo* cestodicidal activity has been evaluated against *Hymenolepis nana* infection in rats. The compound **10** is found to be the most active member of the series showing 66% clearance of infection at a dose of 400 mg/kg for 3 days. Some compounds have also been tested for their antifilarial activity against *Brugia pahangi* in jirds but none of the compound shows any activity.

The search for new structural 'leads' based on the broad spectrum anthelmintic activity associated with salicylanilides[1-3] has resulted in the synthesis of 2',5-dichloro-4'-nitrosalicylanilide (niclosamide)[4] with marked cestodicidal activity. These observations led us to synthesise structurally related β-(2-naphthoxy)-propioanilides (**3-24**) which have been evaluated for their antifilarial and cestodicidal activities. The results are reported in this note.

Treatment of 2-naphthoxypropionic acid (**1**)[5] with disubstituted anilines (**2**) in the presence of PCl_3 in refluxing xylene or toluene gave substituted β-(2-naphthoxy)propioanilides (**3-6**). The β-(2-naphthoxy)-nitropropioanilides (**4-6**) thus obtained, were hydrogenated over Raney-nickel to yield the corresponding β-(2-naphthoxy)-aminopropioanilides (**7-9**) which were smoothly converted into the respective β-(2-naphthoxy)-isothiocyanopropioanilides (**10-12**). Treatment of **10** with piperidine and 3-methylpiperidine afforded **13** and **14** respectively. Nucleophilic reaction of **3** with different cyclic amines yielded **15-24** (Scheme 1).



SCHEME 1

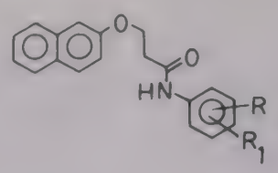
Biological activity

The compounds **10**, **13** and **15-20** were tested for their antifilarial activity against *Brugia pahangi* in jirds (*Meriones unguiculatus*). Each of the jirds was infected by i.p. implantation of *B. pahangi* using the technique of Suswillo and Denham[6]. The test compounds were injected sub-cutaneously suspended in 0.5% Tween 80 on five successive days at 100 mg/kg, given a total dose of 500 mg/kg. None of the compounds showed any activity.

The compounds were also tested for their *in vivo* cestodicidal activity against *Hymenolepis nana* infection in rats by the technique of Steward[7]. The compounds were given orally at 500 and 400 mg/kg doses using three rats per experimental group. For all the control experiments, niclosamide was used as a standard drug which cleared 100% of the above infection at a single oral dose of 50 mg/kg. The results are summarised in Table 1. A preliminary evaluation of anticestode activity against *H. nana* revealed that compounds **10-12** given at a dose of 400 mg/kg for 3 days could induce 60-66% worm expulsion in rats while compounds **3-6**, **16-17** and **21-22** were also found to possess 40-58% activity at a dose of 400 mg/kg for 3 days. Rest of the compounds were found inactive at 500 mg/kg dose. The cestodicidal activity data given in Table 1 clearly indicate that the conversion of an electron attracting group like NO_2 into an electron donating group like NH_2 by reduction renders the compounds inactive. Similarly conversion of −NCS function into piperidinothioamido or 3-methylpiperidinothioamido group causes complete loss of activity. This clearly indicates that the presence of electron withdrawing groups (Cl, NO_2, NCS) in ring-B is an important factor for governing the cestodicidal activity.

An attempt was also been made to establish the quantitative-structure activity relationship using linear free energy related regression analysis. It was observed that the best correlationship is described by the parabolic relationship of lipophilicity (log *P*) with biological activity and the best equation for all the compounds of the series was:

Table 1—Physical Data and Cestodicidal Activity of β-(2-Naphthoxy)propioanilides (3-24)



Compd	R	R_1	m.p. °C	Mol. formula*	Cestocidal activity		Biological activity (log 1/C)	
					Dose (mg/kg)	Efficacy (%)	Obs.	Calc.
3	3-NO_2	4-Cl	152	$C_{19}H_{15}ClN_2O_4$	400	46.0	−0.0696	−0.0749
4	2-Cl	4-NO_2	162-63	$C_{19}H_{15}ClN_2O_4$	400	55.0	0.0872	−0.0749
5	2-OCH_3	4-NO_2	170-71	$C_{20}H_{18}N_2O_5$	400	58.0	0.1402	−0.0213
6	4-Cl	2-NO_2	112	$C_{19}H_{15}ClN_2O_4$	400	40.0	−0.1761	−0.0749
7	2-Cl	4-NH_2	96	$C_{19}H_{17}ClN_2O_2$	500	Inactive	—	—
8	4-Cl	2-NH_2	105-6	$C_{19}H_{17}ClN_2O_2$	—	—	—	—
9	2-OCH_3	4-NH_2	122	$C_{20}H_{20}N_2O_3$	—	—	—	—
10	2-Cl	4-NCS	150	$C_{20}H_{15}ClN_2O_2S$	400	66.0	0.2880	0.2760
11	4-Cl	2-NCS	198	$C_{20}H_{15}ClN_2O_2S$	400	65.0	0.2688	0.2760
12	2-OCH_3	4-NCS	180	$C_{21}H_{18}N_2O_3S$	400	60.0	0.1761	0.2150
13	2-Cl	4-Piperidinothioamido	148	$C_{25}H_{26}ClN_3O_2S$	500	Inactive	—	—
14	2-Cl	4-(3-Methylpiperidinothioamido)	200	$C_{26}H_{28}ClN_3O_2S$	500	Inactive	—	—
15	3-NO_2	4-Pyrrolidinyl	195	$C_{23}H_{23}N_3O_4$	—	—	—	—
16	3-NO_2	4-Piperidinyl	172	$C_{24}H_{25}N_3O_4$	400	40.0	−0.1761	−0.0671
17	3-NO_2	4-(2-Methylpiperidinyl)	167	$C_{25}H_{27}N_3O_4$	400	42.0	−0.1402	0.0215
18	3-NO_2	4-(3-Methylpiperidinyl)	153	$C_{25}H_{27}N_3O_4$	—	—	—	—
19	3-NO_2	4-(4-Methylpiperidinyl)	110	$C_{25}H_{27}N_3O_4$	—	—	—	—
20	3-NO_2	4-Morpholinyl	90	$C_{23}H_{23}N_3O_5$	—	—	—	—
21	3-NO_2	4-(4-Methylpiperazinyl)	82	$C_{24}H_{26}N_4O_4$	400	52.0	0.0348	0.1370
22	3-NO_2	4-(4-Phenylpiperazinyl)	105-6	$C_{29}H_{28}N_4O_4$	400	46.0	−0.0696	−0.6078
23	3-NO_2	4-[4-(3-Chlorophenyl)piperazinyl]	101	$C_{29}H_{27}ClN_4O_4$	—	—	—	—
24	3-NO_2	4-Homopiperidinyl	125-6	$C_{25}H_{27}N_3O_4$	—	—	—	—

*All the compounds gave satisfactory C, H and N analyses (within ±0.5% of the theoretical values).

$$\log 1/C = -0.0623 - 0.0926\,\pi + 0.1476\,\pi^2$$

Structures of all the compounds were established by their IR and PMR spectra recorded respectively on Perkin-Elmer 157 infracord (ν_{max} in cm^{-1}) and Perkin-Elmer R-32 instrument (chemical shifts in δ-scale downfield from TMS as internal standard). The mass spectra were taken on a JEOL JMS D-300 instrument. Melting points were taken in H_2SO_4-bath and are uncorrected.

2′-Chloro-4′-nitro-β-(2-naphthoxy)propio-anilide (**4**)

PCl_3 (0.8 ml, 0.006 mol) was added dropwise to a solution of β-(2-naphthoxy)propionic acid (3.2 g, 0.015 mol) and 2-chloro-4-nitroaniline (2.6 g, 0.015 mol) in toluene (15 ml) under reflux. Refluxing was continued for 2 hr and the reaction mixture cooled, excess of PCl_3 decomposed by adding water and the residual solid crystallized from THF-H_2O to furnish **4**, yield 4.2 g (76.6%), m.p. 162-63 ; IR (KBr): 3300 (NH), 1660 (C=O), 1340, 1515 (NO_2) (Found: C, 61.4; H, 4.0; N, 7.2. $C_{19}H_{15}ClN_2O_4$ requires C, 61.5; H, 4.0; N, 7.6%).

In a similar way other compounds (**3, 5, 6**) were also prepared. Their characterization data are given in Table 1.

4′-Amino-2′-chloro-β(2-naphthoxy)propio-anilide (**7**)

A mixture of **4** (3.7 g, 0.01 mol) and Raney-nickel (1.0 g) in abs. ethanol (50 ml) was refluxed with hydrazine hydrate (5 ml, 99%) for 12 hr, the catalyst removed and the filtrate concentrated to give the product as a solid which crystallised from ethanol, yield 2.8 g (82%), m.p. 96 , IR(KBr): 3400 (NH_2), 3250 (NH), 1650 (C=O) (Found: C, 66.5; H, 4.5; N, 8.0. $C_{19}H_{17}ClN_2O_2$ requires C, 67.0; H, 5.0; N, 8.2%).

Compounds **8-9** were prepared following the above method and their characterization data are given in Table 1.

2′-Chloro-4′-isothiocyano-β-(2-naphthoxy)pro-pioanilide (**10**)

A solution of thiophosgene (1.1 g, 0.01 mol) in dry acetone was added dropwise to a stirred solution of **7**

(3.4 g, 0.01 mol) in dry acetone (100 ml) and the reaction mixture stirred for 10 hr at room temperature. Solvent was removed from the reaction mixture and the residual solid crystallized from THF to give **10**, yield 2.5 g (66%), m.p. 150°; IR (KBr): 3240 (NH), 2040 (NCS), 1650 (C=O) (Found: C, 62.4; H, 3.7; N, 7.0. $C_{20}H_{15}ClN_2O_2S$ requires C, 62.7; H, 3.9; N, 7.3%).

Other isothiocyanates (**11**, **12**) were prepared in a similar manner and their characterization data are given in Table 1.

2′-Chloro-4′-(piperidinothioamido)-β-(2-naphthoxy)propioanilide (**13**)

A solution of **10** (3.8 g, 0.01 mol) in piperidine (0.9 g, 0.01 mol) was heated on a water-bath for 8 hr and poured on crushed ice. The separated solid was filtered and crystallised from ethanol to give **13** (Table 1), yield 3.5 g (76%), m.p. 148°; IR (KBr): 3350 (NH), 1690 (C=O), 1250 (C=S) (Found: C, 63.8; H, 5.3; N, 8.7. $C_{25}H_{26}ClN_3O_2S$ requires C, 64.2; H, 5.6; N, 9.0%).

Compound **14** (Table 1) was prepared in a similar manner.

3′-Nitro-4′-pyrrolidinyl-β-(2-naphthoxy)propioanilide (**15**)

A mixture of **3** (2.8 g, 0.0075 mol) and pyrrolidine (0.7 g, 0.01 mol) in dry pyridine (30 ml) was refluxed for 30 hr, solvent removed from the reaction mixture and the residual solid, obtained after washing the residue with dil. hydrochloric acid, dried and crystallized from acetone to give **15** (Table 1), yield 2 g (65%), m.p. 195°; IR (KBr): 3200 (NH), 1645 (C=O), 1340, 1520 (NO_2); PMR (DMSO-d_6): 1.65-2.00 (*m*, 4H, $-NCH_2CH_2CH_2$), 2.40-2.77 (*m*, 4H, CH_2-N-CH_2), 3.50-3.83 (*m*, 4H, OCH_2CH_2), 6.7-7.4 (*m*,ι, 11H, Ar-*H*, NH); MS: *m/z* 405 (M^+) (Found: C, 68.0; H, 5.4; N, 10.0. $C_{23}H_{23}N_3O_4$ requires C, 68.1; H, 5.7; N, 10.4%).

In a similar way compounds **16-24** (Table 1) were prepared.

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Antiinflammatory, Analgesic & Antibacterial Activities of 4-(2′-Dialkyl/diarylamino-4′-phenyl-5′-thiazolylcarbonyl)-3-arylsydnones

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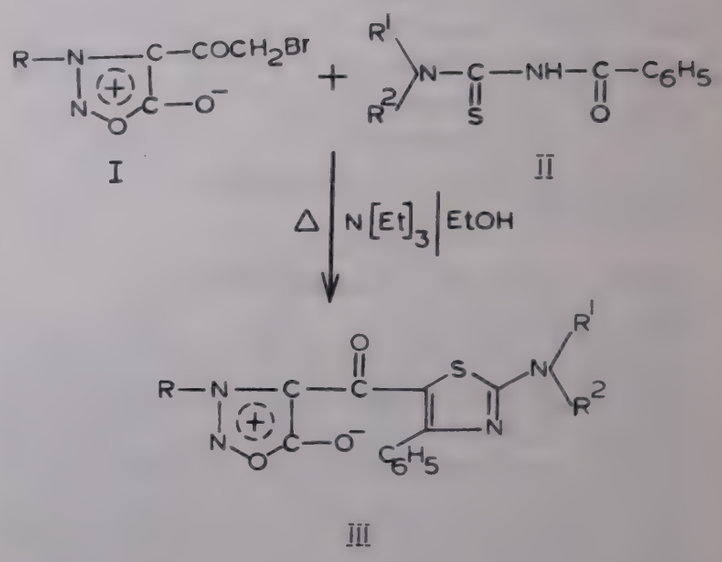
3-Arylsydnones (III) with a thiazole moiety linked through a carbonyl group have been synthesised by treating 3-aryl-4-bromoacylsydnones (I) with N-substituted-N′-benzoylthiourea (II) and screened for their antiinflammatory, analgesic and antibacterial activities. Some of them show promising activities.



In our search for active sydnones and their derivatives, several sydnones with heterocyclic moieties like pyrazole[1], pyrazoline[2], thiazole[3,4], benzofuran, imidazothiazole and imidazopyridine[5] were prepared and screened for their antiinflammatory and analgesic activities. It may be mentioned here that sydnones with a thiazole moiety, though prepared much earlier[6], were not subjected to biological screening. Recently, sydnones with other heterocyclic moieties like, thiadiazole[7], oxadiazole[8] triazole[7] thiophene, benzothiazine, benzoxazine, dihydroquinaxoline have been reported[9,10] but not screened for their biological activities. Since dialkyl/diaryl-aminothiazoles have a wide variety of applications[11], it was though of interest to prepare 3-phenylsydnones with a dialkyl/diarylaminothiazole moiety linked through a carbonyl group in position-4. For the preparation of such compounds 3-aryl-4-bromoacylsydnones (I)[3] were treated with N-substituted-N′-benzoylthioureas (II)[12]. The resulting compounds (III; Table 1) were tested for their antiinflammatory, analgesic and antibacterial activities. The IR† and PMR† spectra of III were in complete agreement with the assigned structures.

The IR spectra of III_{1-32} displayed a strong absorption band at 1740-1750 due to sydnone C=O and that at 1620-1630 due to C=O group present in 4-position of the sydnone ring. These compounds showed another stretching band at 3320-3300 due to N−H function. The PMR spectral data of III exhibited a signal around 7.1-7.4 for the aromatic protons. The O−CH_3 (in III_4, III_8, III_{12}, III_{16}, III_{20}, III_{24}, III_{28} and III_{32}) and N−CH_3 protons (in III_{1-4}) appeared at 3.8 and 3.2 respectively, and the C−CH_3 protons (in III_2, III_6, III_{10}, III_{14}, III_{18}, III_{22}, III_{26} and III_{30}) at 2.4. However, in compounds III_{5-8} containing a morpholino group, the O−CH_2 and N−CH_2 protons appeared at 3.6 and 3.5 respectively.

Antiinflammatory activity

Fourteen compounds were selected from amongst the compounds prepared and tested for their antiinflammatory activity by Carrageenin-induced rat paw edema test according to the procedure of Winter *et al.*[13] Groups of six albino rats of either sex weighing about 150 g were used. Carrageenin (1%, 0.1 ml) was injected into plantar surface of the rat's hind paw, 1 hour after oral administration of the test compound as a gum acacia suspension (100 mg/kg). The edema formation was measured 3 hours after injection and compared with that of Carrageenin-induced for calculation of percentage inhibition.

The highest activity was observed in compounds III_6 and III_{14} which showed 50% and 62% inhibition respectively. The three compounds III_{13}, III_{19} and III_{30} did not have appreciable effects and showed 32%, 33% and 41% inhibition respectively. The compounds III_2, III_{12}, III_{18} and III_{25} showed around 15% inhibition and the compounds III_{23} and III_{26} less than 10% inhibition. However, compounds III_{15}, III_{22} and III_{27} did not show any inhibition. Phenylbutazone showed an inhibition of 60-65% under the experimental conditions at a dose level of 100 mg/kg.

Analgesic activity

As in the above case, albino rats of either sex weighing between 100 and 150 g were chosen. The

† IR ν_{max} in cm^{-1} and PMR chemical shifts in δ, ppm here and

Table 1 — Characterization Data of 4-(2′-Dialkyl/diarylamino-4′-phenyl-5′-thiazolylcarbonyl)-3-arylsydnones (III)

	R	R^1	R^2	Yield (%)	m.p. °C	Mol. formula	Found (%) (Calc.) C	H	N
III_1	Phenyl	Methyl	Phenyl	85	200	$C_{25}H_{18}N_4O_3S$	66.5 (66.1)	4.1 4.0	12.1 12.3)
III_2	*p*-Tolyl	Methyl	Phenyl	80	168	$C_{26}H_{20}N_4O_3S$	67.1 (66.7)	4.7 4.3	12.2 12.0)
III_3	*p*-Chlorophenyl	Methyl	Phenyl	76	158	$C_{25}H_{17}N_4O_3SCl$	61.8 (61.4)	3.7 3.5	11.3 11.5)
III_4	*p*-Methoxyphenyl	Methyl	Phenyl	74	192	$C_{26}H_{20}N_4O_4S$	64.9 (64.5)	4.5 4.2	11.4 11.6)
III_5	Phenyl	Morpholino		82	175	$C_{22}H_{18}N_4O_4S$	61.1 (60.8)	4.2 4.2	12.8 12.9)
III_6	*p*-Tolyl	Morpholino		80	180	$C_{23}H_{20}N_4O_4S$	61.8 (61.6)	4.6 4.5	12.4 12.5)
III_7	*p*-Chlorophenyl	Morpholino		76	188	$C_{22}H_{17}N_4O_4SCl$	56.1 (56.4)	3.7 3.7	11.8 12.0)
III_8	*p*-Methoxyphenyl	Morpholino		71	160	$C_{23}H_{20}N_4O_5S$	59.8 (59.5)	4.3 4.3	11.9 12.1)
III_9	Phenyl	H	Benzyl	75	164	$C_{25}H_{18}N_4O_3S$	66.1 (65.9)	3.6 4.0	12.1 12.3)
III_{10}	*p*-Tolyl	H	Benzyl	68	155	$C_{26}H_{20}N_4O_3S$	66.8 (66.5)	4.6 4.3	12.1 11.9)
III_{11}	*p*-Chlorophenyl	H	Benzyl	66	161	$C_{25}H_{17}N_4O_3SCl$	61.7 (61.2)	3.7 3.5	11.3 11.5)
III_{12}	*p*-Methoxyphenyl	H	Benzyl	65	165	$C_{26}H_{20}N_4O_4S$	64.6 (64.5)	4.4 4.2	11.4 11.6)
III_{13}	Phenyl	H	*p*-Chlorophenyl	74	200	$C_{24}H_{15}N_4O_3SCl$	61.7 (60.7)	3.4 3.2	11.6 11.8)
III_{14}	*p*-Tolyl	H	*p*-Chlorophenyl	70	205	$C_{25}H_{17}N_4O_3SCl$	61.3 (61.4	3.2 3.5	11.3 11.5)
III_{15}	*p*-Chlorophenyl	H	*p*-Chlorophenyl	67	197	$C_{24}H_{14}N_4O_3SCl_2$	56.7 (56.6)	3.1 2.8	10.7 11.0)
III_{16}	*p*-Methoxyphenyl	H	*p*-Chlorophenyl	60	214	$C_{25}H_{17}N_4O_4SCl$	59.6 (59.5)	3.6 3.4	10.8 11.0)
III_{17}	Phenyl	H	3,4-Dichlorophenyl	77	185	$C_{24}H_{14}N_4O_3SCl_2$	56.8 (56.6)	2.8 2.8	10.8 11.0)
III_{18}	*p*-Tolyl	H	3,4-Dichlorophenyl	72	168	$C_{25}H_{16}N_4O_3SCl_2$	57.6 (57.4)	3.2 3.1	10.5 10.7)
III_{19}	*p*-Chlorophenyl	H	3,4-Dichlorophenyl	68	198	$C_{24}H_{13}N_4O_3SCl_3$	53.2 (53.0)	2.9 2.4	10.1 10.3)
III_{20}	*p*-Methoxyphenyl	H	3,4-Dichlorophenyl	61	196	$C_{25}H_{16}N_4O_4SCl_2$	56.1 (55.7)	3.2 3.0	10.1 10.4)
III_{21}	Phenyl	H	2,4-Dichlorophenyl	74	196	$C_{24}H_{14}N_4O_3SCl_2$	56.8 (56.6)	3.2 2.8	10.9 11.0)
III_{22}	*p*-Tolyl	H	2,4-Dichlorophenyl	70	210	$C_{25}H_{16}N_4O_3SCl_2$	57.5 (57.4)	3.0 3.1	10.6 10.7)
III_{23}	*p*-Chlorophenyl	H	2,4-Dichlorophenyl	65	201	$C_{24}H_{13}N_4O_3SCl_3$	53.3 (53.0)	2.5 2.4	10.2 10.3)
III_{24}	*p*-Methoxyphenyl	H	2,4-Dichlorophenyl	58	190	$C_{25}H_{16}N_4O_4SCl_2$	55.9 (55.7)	3.2 3.0	10.2 10.4)
III_{25}	Phenyl	H	2,3-Dichlorophenyl	76	192	$C_{24}H_{14}N_4O_3SCl_2$	56.9 (56.6)	3.3 2.8	10.8 11.0)
III_{26}	*p*-Tolyl	H	2,3-Dichlorophenyl	71	193	$C_{25}H_{16}N_4O_3SCl_2$	57.6 (57.4)	3.2 3.1	10.7 10.7)
III_{27}	*p*-Chlorophenyl	H	2,3-Dichlorophenyl	64	191	$C_{24}H_{13}N_4O_3SCl_3$	53.4 (53.0)	2.6 2.4	10.2 10.3)
III_{28}	*p*-Methoxyphenyl	H	2,3-Dichlorophenyl	57	178	$C_{25}H_{16}N_4O_4SCl_2$	55.8 (55.7)	3.3 3.0	10.2 10.4)
III_{29}	Phenyl	H	2,5-Dichlorophenyl	72	178	$C_{24}H_{14}N_4O_3SCl_2$	56.9 (56.6)	3.3 2.8	10.9 11.0)
III_{30}	*p*-Tolyl	H	2,5-Dichlorophenyl	66	185	$C_{25}H_{16}N_4O_3SCl_2$	53.4 (57.4)	2.6 3.1	10.1 10.7)

(Contd.)

Table 1 — Characterization Data of 4-(2'-Dialkyl/diarylamino-4'-phenyl-5'-thiazolylcarbonyl)-3-arylsydnones (III) — (*Contd*)

	R	R^1	R^2	Yield (%)	m.p. °C	Mol. formula	Found (%) (Calc.) C	H	N
III_{31}	*p*-Chlorophenyl	H	2,5-Dichloro-phenyl	64	172	$C_{24}H_{13}N_4O_3SCl_3$	53.4 (53.0	2.9 2.4	10.1 10.3)
III_{32}	*p*-Methoxyphenyl	H	2.5-Dichloro-phenyl	61	182	$C_{25}H_{16}N_4O_4SCl_1$	55.9 (55.7	3.3 3.0	10.3 10.4)

compounds were evaluated by the rat tail flick test according to the method of Finney *et al.*[14] The compound III_6 showed 45% inhibition. The compounds III_{14}, III_{19} and III_{23} showed 40% inhibition, the compounds III_{26} and III_{30} 30% inhibition and the compounds III_{13} and III_{22} 20% inhibition. However, compounds III_{15} and III_{27} showed no inhibition. The standard used was acetylsalicylic acid which showed 70-80% inhibition.

Antibacterial activity

Antibacterial activity of all the 32 compounds was carried out against the gram positive and gram negative pathogenic organisms, viz. *Staphylococcus aureus* and *E. coli*, by the cup-plate method[15] at a concentration of 100 μg/0.1 ml in DMSO. The standards used were sulphanilamide and phenol in DMSO and in the same concentration as above. The zone of inhibition was measured after 24 hr in mm. All the compounds were more active than the standards used. Against the gram positive organisms, compounds III_1, III_2, III_4, III_5, III_8, III_{14}, III_{21}, III_{28}, III_{29} and III_{31} showed maximum inhibition (40 to 50 mm), compounds III_3, III_6, III_7, III_{9-13}, III_{19}, III_{26} and III_{32} showed an inhibition zone of 30 to 40 mm and compounds III_{15}, III_{18}, III_{20}, III_{22-25} and III_{30} 20-30 mm. Against the gram negative organisms, compounds III_{1-3}, III_{7-10}, III_{12}, III_{14}, III_{19}, III_{24}, III_{26}, III_{28}, III_{30} and III_{32} showed an inhibition zone of 30 to 40 mm and compounds III_{4-6}, III_{11}, III_{13}, III_{15-18}, III_{20-23}, III_{25}, III_{29} and III_{31} 20-30 mm. Compound III_{27} showed less than 20 mm zone of inhibition against both the gram positive and gram negative organisms. Sulphanilamide showed 20 mm zone of inhibition against the gram positive and 14 mm against the gram negative organisms. Phenol showed 17 mm zone of inhibition against the gram positive and 14 mm against the gram negative organisms under the experimental conditions at a concentration of 100 μg/0.1 ml. The solvent DMSO showed no activity against *S. aureus* but against *E. coli* it showed an inhibition zone of 12 mm.

Melting points were determined in open capillary tubes and are uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer 221 infrared spectrophotometer and PMR spectra ($CDCl_3$) at 90 MHz on a varian instrument using TMS an internal standard.

4-(2'-Dialkyl/diarylamino-4'-phenyl-5'-thiazolylcarbonyl)-3-arylsydnones (III)

An intimate mixture of I (0.2 mol) and N-substituted-N'-benzoylthiourea (II; 0.2 mol) in dry ethanol was refluxed for 20 min, triethylamine (5 ml) added to it and the reaction mixture refluxed for another 30 min. Thereafter, it was poured into cold water (100 ml) and the resultant solid filtered and recrystallised from ethanol. The characterization data of III are given in Table 1.

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2′-Hydroxychalcone Analogs of 5-Nitrofurfural & Their Antibacterial Activity

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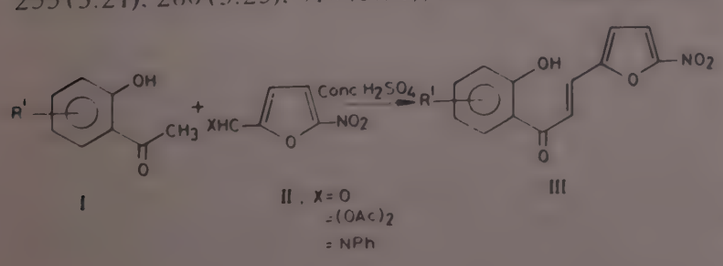
2-Hydroxyacetophenones (I) react with 5-nitrofurfural (II; X = O) under acid-catalysed conditions to give 2′-hydroxychalcone analogs (III). None of these compounds (III) is found to exhibit significant antibacterial and antifungal activities except 1-(2-hydroxyphenyl)-3-(5-nitro-2-furyl)-2-propen-1-one (IIIa) which shows 100% inhibition against *A. niger* at 10 ppm concentration.

1,3-Diaryl-2-propen-1-ones with halogen[1], hydroxy[2], nitro and methoxy[3] substitutions are known to exhibit carcinogenic[1], bactericidal, fungicidal, germicidal[4-6], insecticidal and anti-tubercular[6,7] activities. In view of these physiological properties of substituted propenones and the reported antimicrobial[8,9], antiviral[10] and antitumour[11] activities of nitrofurans, the synthesis of the title compounds has not been taken up with a view to studying their antimicrobial activity.

2-Hydroxyacetophenone (I; R′ = 5-Me) and 5-nitrofurfural (II; X = O) or 5-nitrofurfural diacetate [II; X = $(OAc)_2$] were dissolved in gl. acetic acid by warming on a water-bath and a few drops of conc. sulphuric acid were added to it after cooling to 0-5°C. The mixture was allowed to stand for 4-5 days at room temperature and IIIb (R′ = 5-Me) worked-out by passing through a column of silica gel using a benzene-pet. ether (2:3) as eluent. It crystallised from benzene as orange needles (m.p. 164°); gave a single spot on TLC and analysed for $C_{13}H_9O_3N$. It also gave a wine-red colouration with ethanolic $FeCl_3$. Its IR (KBr) spectrum exhibited absorption bands at 1640 (α, β unsaturated >C=O), 3145 (chelated phenolic OH[12]), 1560 and 1350 cm^{-1} (nitro group). In UV (MeOH) spectrum, it showed absorptions[13] at 230 (log ε 3.18), 255 (3.21), 280 (3.25), 310 (3.31), 370 (3.70) and 445 nm (3.27). The PMR (60 MHz, $CDCl_3$) spectrum of IIIb displayed signals at δ 7.08 and 7.36 (each *s*, 2H, −CH=CH−), 12.83 (*s*, 1H, strongly chelated phenolic OH), 6.91-6.93 and 7.43-7.50 (each *d*, 2H, β,β′-protons of 5-nitro-2-furyl moiety), 2.41 (*s*, 3H, C_5−Me), 7.75-7.83 (*m*, 3H, Ar−*H*). In the mass spectrum it showed the molecular ion at *m/z* 273 (50%) besides the significant peaks at *m/z* 135 (77; *o*-hydroxybenzoyl ion), 134 (69%; RDA fragmentation), 227 (100%; M − NO_2, as usual in nitro compounds[14]) and 161 (84%; 4-hydroxy-chromenyl ion, commonly observed in chromanones[15]).



It was observed that like the corresponding furfural diacetate, the schiff base (II; X = NPh) of 5-nitrofurfural was also stable at room temperature and underwent condensation with I under similar conditions giving the compounds identical (m.m.p and IR) with those obtained by the above method. Out of the nine compounds prepared solitary member (IIIa, R −H) was reported earlier[16].

All the compounds synthesized had spectral data (IR, UV, PMR, mass) similar to those of IIIb. Their characterization data are given in Table 1.

Antimicrobial activity

The antibacterial and antifungal activities of the compounds were determined against the bacteria *E. coli* and *Staphylococcus aureus* and the fungus *Aspergillus niger*. None of the compounds was found to be significantly active against the bacteria. However, 1-(2-hydroxyphenyl)-3-(5-nitro-2-furyl)-2-propen-1-one (IIIa, R′ = H) showed 100% inhibition against *A. niger* at 10 ppm and 45% inhibition at 2 ppm concentrations.

Melting points were taken in open capillaries in a sulphuric acid-bath and are uncorrected. IR spectra were recorded on a Perkin-Elmer infracord-337 instrument, UV spectra on a Beckmann DB instrument, PMR spectra on a Varian A60D instrument and mass spectra on a Hitachi RMU 6L mass spectrometer.

1-(2-Hydroxyphenyl)-3-(5-nitro-2-furyl)-2-propen-1-ones (III): General procedure

To a solution of 5-nitrofurfural (II, 0.005 mol) in gl. acetic acid (10 ml), prepared by warming on a water-bath and then cooled to 0-5°C in an ice-bath, was added the appropriate 2-hydroxy-acetophenone (I, 0.004 mol) in small portion under stirring. After the addition of I was over, conc. sulphuric acid (0.5 ml) was added and the reaction mixture allowed to stand at

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Table 1 – Characterization Data of 1-(2-Hydroxy)-3-(5-nitro-2-furyl)-2-propen-1-ones (III)

Compd	R′	Yield (%)	m.p. °C	Mol. formula	Found (%) (Calc.)		
					C	H	N
IIIa	H	45	166	$C_{13}H_9O_5N$	60.1 (60.2	3.4 3.5	5.3 5.4)
IIIb	5-CH_3	52	164	$C_{14}H_{11}O_5N$	61.5 (61.5	4.1 4.0	5.0 5.1)
IIIc	4-CH_3	47	170	$C_{14}H_{11}O_5N$	61.5 (61.5	4.1 4.0	5.0 5.1)
IIId	3-CH_3	40	140	$C_{14}H_{11}O_5N$	61.4 (61.5	4.1 4.0	5.0 5.1)
IIIe	5-Cl	47	164	$C_{13}H_8O_5NCl$	53.0 (53.2	2.6 2.7	4.6 4.7)
IIIf	3-Cl	43	202	$C_{13}H_8O_5NCl$	53.0 (53.1	2.7 2.7	4.6 4.7)
IIIg	3,5-Dichloro	40	195	$C_{13}H_7O_5NCl_2$	47.6 (47.6	2.1 2.1	4.3 4.3)
IIIh	4-OH	41	320	$C_{13}H_9O_6N$	56.6 (56.7	3.3 3.3	5.0 5.1)
IIIi	4-OMe	43	220	$C_{14}H_{11}O_6N$	58.2 (58.1	3.7 3.8	4.9 4.8)

room temperature for 4-5 days. The brown solid obtained after transferring the reaction mixture into ice water was passed through a column of silica gel using benzene-pet. ether (2:3) as eluent and recrystallised from benzene as orange needles.

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Synthesis & Biological Evaluation of Some DDT Analogues

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Some DDT analogues (I-III) have been prepared by replacing the two chlorine atoms in the aromatic rings by bioactive, selective and biodegradable groups such as unsaturated hydrocarbon chains, epoxide and crown ether rings. The biological activity of these compounds has been determined against various insects and the data indicate that larger substitutions in the DDT molecule cause loss of activity. Their structure elucidation is based on elemental analysis and spectral (IR and PMR) data.

2,2-Bis(*p*-chlorophenyl)-1,1,1-trichloroethane (DDT) has a wide spectrum of biological activity against different families of insects and related organisms. For the biodegradable analogoues of DDT molecule so far examined, reliance has been mainly on the balance between biological dehydrochlorination and oxidation. The oxidation (hydroxylation) process is well established for DDT analogues, but the removal of chlorine is generally more difficult[1,2]. The *p,p'*-chlorine substituents in the DDT molecule can be replaced by other groups yielding the compounds of comparable activity. The unsubstituted compound, is however, of very low activity and the *p,p'*-dihydroxy compound is quite inactive. The *p,p'*-dibromo and diethyl compounds do not have adequate activity to justify their higher cost. The only *p,p'*-analogue to have achieved an important commercial position is the dimethoxy compound, called methoxychlore. It is not as active as DDT, but is more vulnerable to biochemical attack so that it has much less tendency to accumulate in fat depots.

The above facts prompted us to prepare some DDT analogues, which might have better activities than the parent molecule DDT, by incorporating some bioactive moieties and carry out a preliminary investigation to evaluate their biological effects.

Three analogues (I-III) of DDT were synthesised by replacing the chlorine atoms in the aromatic rings by bioactive, selective and biodegradable groups such as the unsaturated hydrocarbon chains (allyl and geranyl), the epoxide and the crown ether rings. Thus, 2,2-bis(*p*-hydroxyphenyl-1,1,1-trichloroethane on treatment with geranyl bromide in the presence of sodium ethoxide afforded yellow crystals of 2,2-bis(*p*-geranyloxyphenyl)-1,1,1-trichloroethane (I). Compound II was obtained as a result of two sequence reactions. Treatment of 2,2-bis(*p*-hydroxyphenyl)-1,1,1-trichloroethane with allyl bromide in the presence of sodium ethoxide led to the formation of 2,2-bis(*p*-allyloxyphenyl)-1,1,1-trichloroethane which on oxidation with chlorobenzoic acid gave 2-(*p*-allyoxyphenyl)-2-[*p*-(2,3-epoxypropoxy)-phenyl]-1,1,1-trichloroethane (II). Reaction of benzocrown ether with chloral hydrate in the presence of sulphuric acid led to the formation of 1,1,1-trichloro-2,2-bis-[3,4-(3,6,9-trioxaundecamethylenedioxy)-phenyl]ethane (III)[3].

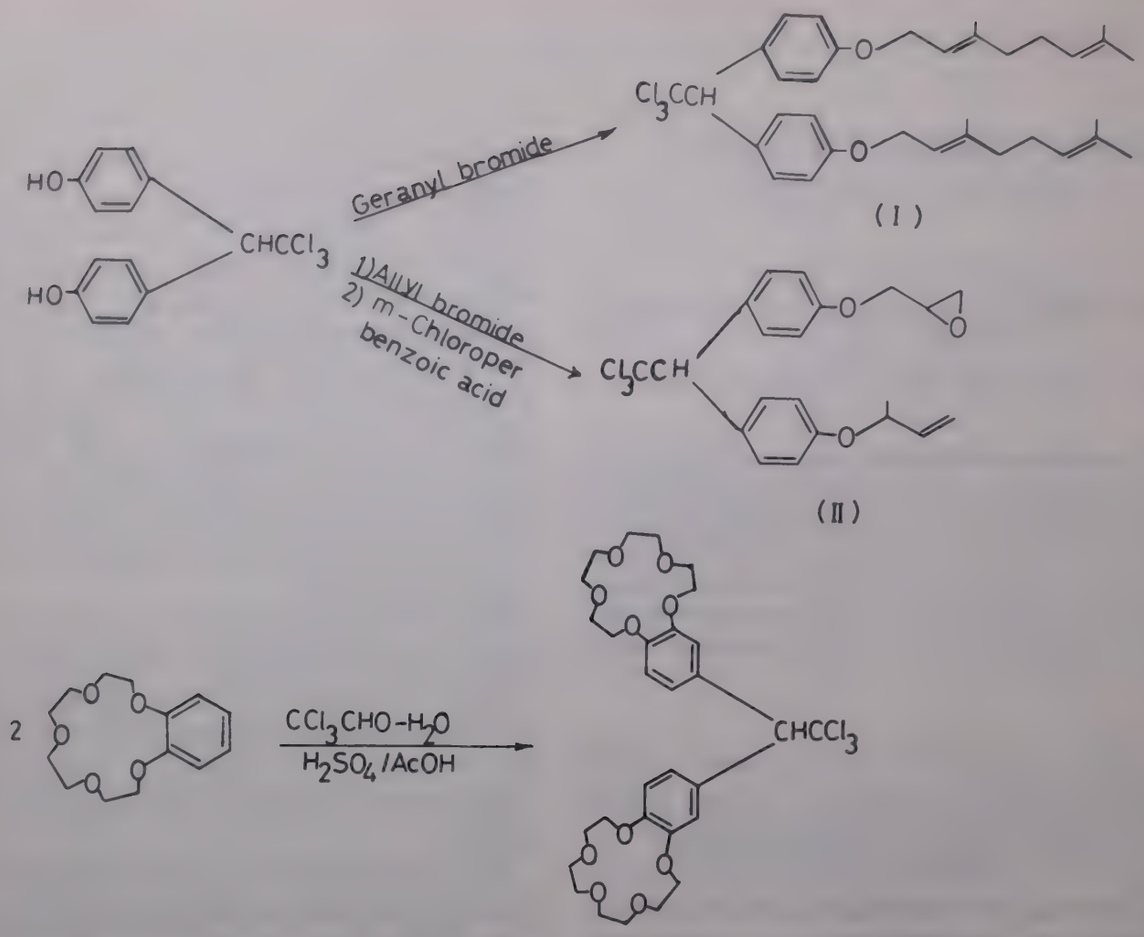
The DDT analogues I-III were examined for their insecticidal, antifeeding and chemosterilant effects on various insect species. Their toxicological action was also determined in order to obtain information about the changes in the biological activity caused by variation in the aromatic rings of the parent molecule (DDT).

The DDT analogues were also investigated for their antiinsect hormone action on the house fly (as anti-ecdsone and as chemosterilant). The results of biological activity (Table 1) indicate that none of the three analogues tested have any interfering capacity with the insect hormone system as well as with their anti-feeding and insecticidal action. The inactivity of these DDT analogues as antiinsect agents in general

Table 1—Anti-feeding Data of Some DDT Analogues on Various Insect Species

Compound	Insect species	Anti-feeding effect*
I	*Leptinotarsa decemlineata* (4th instar larva)	0
	Leptinotarsa decemlineata (adult)	0
	Pieris brassicae	+ + +
	Momestra brassicae	0
II	*Leptinotarsa decemlineata* (4th instar larva)	0
	Leptinotarsa decemlineata (adult)	+
	Pieris brassicae	0
	Momestra brassicae	0
III	*Leptinotarsa decemlineata* (4th instar larva)	+ +
	Leptinotarsa decemlineata (adult)	+
	Pieris brassicae	0
	Momestra brassicae	0

*0 = No effect; + = weak; + + = medium; + + + = good



and as antiinsect hormone compounds in particular, suggests that substitution of the *p,p'*-chloro groups in the DDT molecule by larger groups, although they may be bio-active moieties, causes loss of activity.

Melting points are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 577 grating spectrometer, and 60 MHz PMR spectra in $CDCl_3$ on a JEOL 60-HL instrument at room temperature using TMS as internal standard. The biological activities were determined by the procedures reported earlier[4,5].

2,2-Bis(p-geranylphenoxy)-1,1,1-trichloroethane (I)

To a solution of 2,2-bis(*p*-hydroxyphenyl)-1,1,1-trichloroethane (3.1 g, 0.01 mol) in ethanol (10 ml) was added sodium ethoxide (0.5 g, Na in 10 ml ethanol), and then geranyl bromide (4.3 g, 0.02 mol) added to it drop by drop. Thereafter, the reaction mixture was refluxed for 4 hr, allowed to stand at room temperature for 1 hr, solvent removed and water added to dissolve the salt formed. The whole mixture was kept under cooling overnight and the resultant precipitate filtered, dried and crystallized from ethanol to give yellow crystals of I, m.p. 78-80°, yield 82% (Found: C, 69.2; H, 7.2; Cl, 18.2. $C_{34}H_{41}O_2Cl_3$ requires C, 69.0; H, 7.3; Cl, 18.3%); IR: 750 (Cl_3OH), 1250 cm^{-1} (ether linkage).

2-(p-Allyloxyphenyl)-2-[p-(2,3-epoxypropoxy)phenyl]-1,1,1-trichloroethane (II)

To a mixture of 2,2-bis(*p*-hydroxyphenyl)-1,1,1-trichloroethane (3.1 g, 0.01 mol) in ethanol (10 ml) and a solution of sodium ethoxide (0.46 g, sodium in 10 ml ethanol) under reflux, was added allyl bromide (2.4 g, 0.02 mol) dropwise, and the reaction mixture refluxed for 30 min. After the removal of solvent, water was added to dissolve the salt formed. The resultant white precipitate was filtered and crystallized from ethanol to give white crystals of 2,2-bis(*p*-allyloxyphenyl)-1,1,1-trichloroethane (2.7 g, 0.007 mol). The latter compound was added to a solution of *m*-chlorobenzoic acid (2.83 g, 0.016 mol) in dichloroethane (25 ml) and the reaction mixture stirred at room tettemperature until the precipitation of benzoic acid was complete. Thereafter, the reaction mixture was filtered, washed with sodium bicarbonate solution and then with water, dried (anhyd. sodium sulphate), solvent removed and the residue kept under cooling overnight. A yellow viscous material was formed which on addition of pet. ether (100-120°) gave a yellow solid. It crystallized from ethanol to give II in yellow crystals, m.p. 63-65°, yield 80% (Found: C, 55.6, H, 4.5; Cl, 24.9. $C_{20}H_{19}O_3Cl_3$ requires C, 55.7; H, 4.4; Cl, 25.0%); IR: 1605, 1505, 835 (aromatic rings), 1645, 990, 910 (acidic allyl), 735 (trichloromethyl group), 1250 cm^{-1} (ether linkage); PMR: 2.70 (*d*, 2H, CH_2), 3.30 (*m*, 1H, CH), 4.05 (*dd*, 2H, OCH_2), 4.45 (*d*, 2H, allyl OCH_2), 5.2-5.35 (*d*, 2H, $-CH_2$), 5.95 (*m*, 1H, $-CH$), 4.90 (*s*, 1H, Ar$-CH-$Ar), 6.86-7.50 (*m*, 8H, Ar$-H$).

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Reactions of *o*-Aminothiophenol, Guanidine, Thiourea, Hydrazine Hydrate & Hydroxylamine with Acryloylthiazoles & Microbial Activities of the Reaction Products

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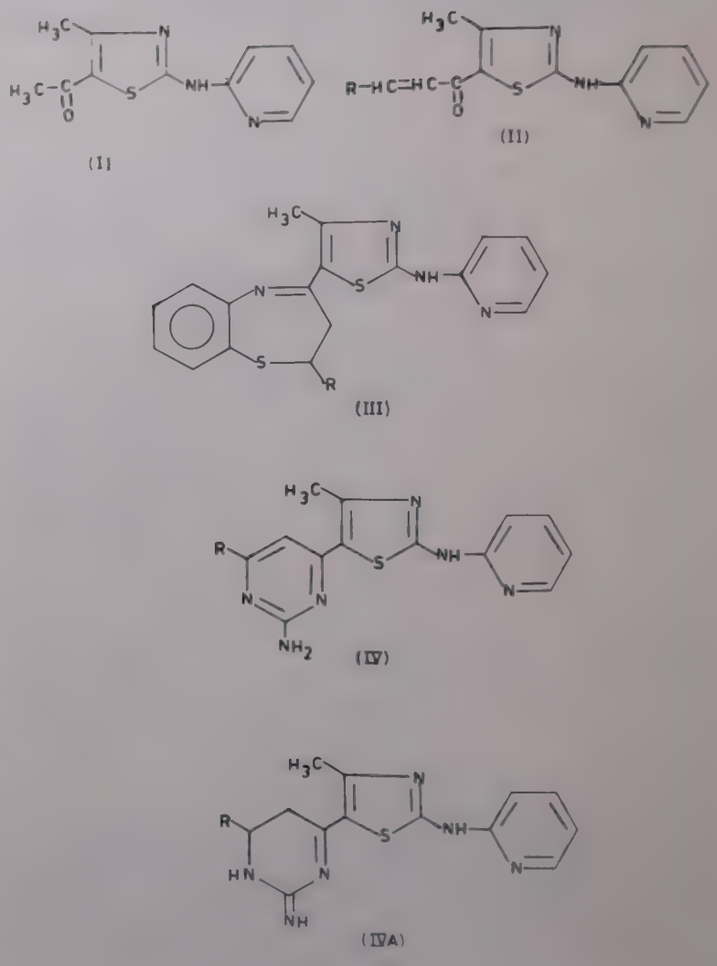
5-(3′-Heterylacryloyl)-4-methyl-2-(2′-pyridylamino)thiazoles (II) have been synthesized by the Claisen-Schmidt condensation of 5-acetyl-4-methyl-2-(2′-pyridylamino)thiazole (I). The acryloylthiazoles (II) react with *o*-aminothiophenol, guanidine, thiourea, hydrazine hydrate and hydroxylamine to give thiazolylbenzothiazepines (III), thiazolylaminopyrimidines (IV), thiazolyl-2-thiopyrimidines (V), thiazolylpyrazolines (VI) and thiazolylisoxazolines (VII), respectively.

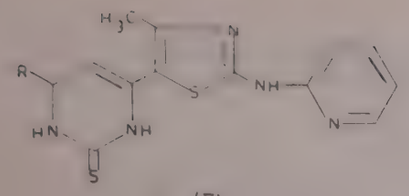
The use of thiazole in curative treatments has been firmly established[1]. Recently Mane *et al.* have synthesized acryloylthiazoles and studied their microbial activity[2]. The heterocyclic nuclei such as aminopyrimidines[3], thiopyrimidines[4-6], isoxazolines[7,8], pyrazolines[9,10] and benzothiazepines[11-15] possess remarkable biological activities. The biological activities of these nuclei and earlier interest in incorporating heteryl moieties in thiazoles have prompted us to synthesize some new thiazoles bearing aminothiopyrimidinyl, isoxazolinyl, pyrazolinyl and benzothiazepinyl moieties.

In the present investigation 5-(3′-heterylacryloyl)-4-methyl-2-(2′-pyridylamino)thiazoles (II) have been obtained by the Claisen-Schmidt condensation of 5-acetyl-2-(2′-pyridyl-amino)-4-methylthiazole[2] (I) and heteryl aldehydes. The desired 2-heteryl-4-substituted-thiazolyl-3,4-dihydro-1,5-benzothiazepines (III) were prepared by reacting II with *o*-aminothiophenol in ethanol in the presence of piperidine followed by cyclisation with AcOH. Their structures were established by elemental and spectral studies. The IR spectra of III displayed bands at 1610-1625 (C=N), 3325-3410 (amino str.) and 1550-1560 (−NH bending) besides those characteristic of thiazole nucleus in the regions 1540-1570, 1420-1460, 1350-1380 and 800-830 cm^{-1}. Their structures were further supported by their PMR spectra which displayed signals at δ 2.27 (*s*, 3H, CH_3), 3.0-3.2 (*m*, 2H, $-CH_2-CH$), 5.0-5.8 (*dd*, 1H, J = 11 Hz and 5 Hz, CH_2-CH) and 7.0-7.8 (*m*, 11/12 H, Ar−H). The signals due to secondary amino proton were not observed up to δ 8.5.



The reaction of II with guanidine hydrochloride in ethanolic KOH produced the corresponding 6-(substituted-thiazolyl)-4-heteryl-2-aminopyrimidines (IV). This might proceed either by a route[16] involving 1,4- or 1,2-addition of guanidine to chalcone (II) followed by cyclisation of the intermediate to give IVA. The latter undergoes proton shift and aromatisation to yield the 2-aminopyridimines (IV). The structural assignments were based on spectral data; IR: 1670-1620 and 1605-1540 cm^{-1} (characteristic absorptions of pyrimidine system), 3400-3525 (two bands, amino str.) and characteristic absorptions due to thiazole nucleus; PMR: δ 2.74 (*s*, 3H, CH_3), 5.43-5.65 (broad, 2H, NH_2), 7.8-8.0 (*s*, 1H, $-C=CH-$) and 6.8-7.9 (*m*, 7/8H, Ar−*H*).

Compounds II on reaction with thiourea in ethanolic KOH under reflux for 2-3 hr yielded the corresponding 6-heteryl-3,4-dihydro-4-(substituted thiazolyl)pyrimidine-2-(1*H*)thiones (V) and not the 6-heteryl-5,6-dihydro-4-(substituted thiazolyl)pyrimidine-2-(1*H*)-thiones (VA). The reaction proceeds either[17] by 1,2- or 1,4-addition of the anion to the ketone followed by cyclisation of the intermediate. The



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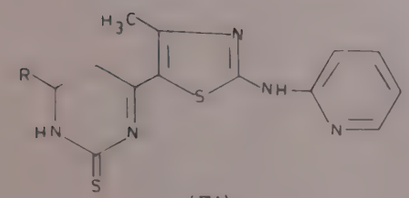

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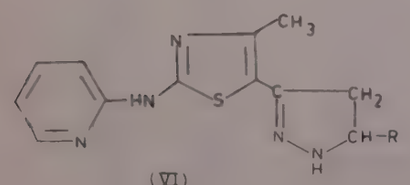

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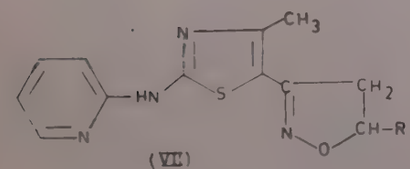

(VII)

structure of V was established by spectral data; IR: 1220 (C=S), 1620 (C=N), 3400-3500 cm^{-1} (broad NH), thiazole ring absorptions and no absorptions due to mercapto group (ruled out enolic isomers); PMR: δ 2.67 (*s*, 3H, CH_3), 5.07-5.22 (*dd*, 2H, CH−CH=), 7.0-7.65 (*m*, 7/8H, Ar−*H*) and 7.85-8.0 (broad, 2H, 2NH, exchangeable with D_2O).

The compounds II were allowed to react with hydrazine hydrate in gl. AcOH to give the corresponding 5-heteryl-3-[4′-methyl-2′-(2″-pyridylamino)thiazol-5′-yl]-Δ^2-pyrazolines (VI). The formation of VI takes place probably via 1,2-addition of hydrazine hydrate to the carbonyl group of II followed by dehydration cyclisation and rearrangement. The structure assigned to VI was further supported by IR and PMR spectra; IR: 3200-3500 (broad, NH), 1620-1640 (C=N), 1560 (NH bending) and characteristic absorptions of thiazole ring; PMR: δ 2.65 (*s*, 3H, CH_3), 3.3-5.5 (*ABX* pattern, 3H, −CH−CH_2− of pyrazoline ring) and 7.0-7.6 (*m*, 7/8H, Ar−*H*).

Compounds II also reacted with hydroxylamine in ethanolic KOH to give 5-heteryl-3-[4′-methyl-2′-(2″-pyridylamino)thiazol-5′-yl]-Δ^2-isoxazolines (VII), probably via 1,2-addition mechanism[18]. The structures of VII were consistent with their IR and PMR spectra; IR: 3250-3400 (broad, NH), 1620-1630 (C=N), 1230 cm^{-1} (C−O−N) and usual thiazole absorptions; PMR: δ 2.6 (*s*, 3H, CH_3), 3.5-6.0 (*ABX* pattern, 3H of dihydro isoxazole protons) and 7.1-7.8 (*m*, 7/8H, Ar−H).

Microbial screening

All the compounds were screened for their fungicidal activity against *Penicillium janthelium* at 25° at 500 ppm concentration by the dry weight technique. Except Vd, all the compounds were found to be active. Among the compounds tested, IVd possessed excellent inhibition property.

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in nujol mull on a Beckman IR spectrophotometer, the PMR spectra in $CDCl_3$ on a Varian F 60 spectrometer using TMS as internal standard.

4-*Methyl*-2-(2′-*pyridylamino*)-5-[3′-(2″-*thienyl*)*acryloyl*]*thiazole* (*IId*)

A mixture of I (2.33 g, 0.01 mol), thiophen-2-aldehyde (1.12 g, 0.01 mol) and ethanol (20 ml) was cooled in an ice bath to about 10°. To the cold solution was added dropwise 50% aq. KOH solution (15-20 ml) and the reaction mixture allowed to stand for 12 hr at room temperature. It was then poured into ice water, neutralised with AcOH and the precipitated solid filtered washed with water and crystallized from ethanol, m.p. 212°. Compounds IIa-c were similarly prepared and gave red colouration with conc. H_2SO_4. Their characterization data are given in Table 1.

2,3-*Dihydro*-4-[4′-*methyl*-2′-(2″-*pyridylamino*)-*thiazol*-5′-*yl*]-2-(2′-*thienyl*)-1,5-*benzothiazepine* (*IIId*)

4-Methyl-2-(2′-pyridylamino)-5-[3′-(2″-thienyl)-acryloyl]thiazole (IId; 3.2 g, 0.01 mol), *o*-amino-thiophenyl (1.37 g, 0.011 mol) and few drops of piperidine were refluxed in ethanol (50 ml) for 4 hr. Thereafter, gl. acetic acid (10 ml) was added to the reaction mixture and heating continued further for 2 hr. It was then cooled, left overnight and resultant solid filtered and crystallised from ethanol. The compounds IIIa, IIIb and IIIc were similarly prepared and their characterization data are given in Table 1.

2-*Amino*-4-(2′-*furyl*)-6-[4′-*methyl*-2′-(2″-*pyridylamino*)*thiazol*-5′-*yl*]*pyrimidine* (*IVa*)

A mixture of 4-methyl-2-(2′-pyridylamino-5-[3′-(2″-furyl)acryloyl]thiazole (IIa; 2.99 g, 0.01 mol), guanidine solution in ethanol (20 ml) and KOH (1.12 g, 0.02 mol) in ethanol was heated under reflux for 5 hr, cooled and poured into ice water containing acetic acid (50 ml). The resultant solid was filtered and crystallised from ethanol, m.p. 170°. Compounds IVb, IVc and

Table 1 – Characterization Data of Acrylothiazoles (II), 1,5-Benzothiazepines (III), Aminopyrimidines (IV), Thiopyrimidines (V), Pyrazolines (VI) and Isoxazolines (VII)

Compd	R	m.p. C	Yield (%)	Mol. formula	N(%)	
					Found	Calc.
IIa	2-Furyl	218	70	$C_{15}H_{13}N_3O_2S$	14.7	14.5
IIb	3-Pyridyl	205	80	$C_{16}H_{14}N_4OS$	18.3	18.1
IIc	4-Pyridyl	217	85	$C_{16}H_{15}N_4OS$	18.3	18.1
IId	2-Thienyl	212	86	$C_{15}H_{13}OS_2$	13.9	13.8
IIIa	2-Furyl	90	50	$C_{22}H_{18}N_4S_2O$	13.0	13.4
IIIb	3-Pyridyl	220	54	$C_{23}H_{19}N_5S_2$	17.2	17.6
IIIc	4-Pyridyl	225	65	$C_{23}H_{19}N_5S_2$	17.5	17.6
IIId	2-Thienyl	143	70	$C_{22}H_{18}N_4S_3$	12.6	12.9
IVa	2-Furyl	170	60	$C_{17}H_{14}N_6SO$	24.9	24.0
IVb	3-Pyridyl	215	50	$C_{18}H_{15}N_7S$	27.0	27.2
IVc	4-Pyridyl	210	68	$C_{18}H_{15}N_7S$	27.5	27.2
IVd	2-Thienyl	200	60	$C_{17}H_{14}N_6S_2$	22.2	23.0
Va	2-Furyl	200	50	$C_{17}H_{15}N_5S_2O$	18.4	19.0
Vb	3-Pyridyl	215	55	$C_{18}H_{16}N_6S_2$	23.3	23.1
Vc	4-Pyridyl	198	72	$C_{18}H_{16}N_6S_2$	23.8	23.1
Vd	2-Thienyl	200	76	$C_{17}H_{15}N_5S_3$	18.3	18.2
VIa	2-Furyl	205	60	$C_{16}H_{14}N_5SO$	21.3	21.6
VIb	3-Pyridyl	225	65	$C_{17}H_{15}N_6S$	20.2	20.8
VIc	4-Pyridyl	233	75	$C_{17}H_{15}N_6S$	20.6	20.8
VId	2-Thienyl	207	80	$C_{16}H_{14}N_5S_2$	20.0	20.6
VIIa	2-Furyl	145	48	$C_{16}H_{14}N_4SO_2$	17.4	17.2
VIIb	3-Pyridyl	228	59	$C_{17}H_{15}N_5SO$	21.6	21.2
VIIc	4-Pyridyl	215	73	$C_{17}H_{15}N_5SO$	21.1	21.2
VIId	2-Thienyl	207	70	$C_{16}H_{14}N_4S_2O$	16.3	16.0

IVd were prepared similarly and their characterization data are given in Table 1.

3,4-*Dihydro*-6-[4′-*methyl*-2′-(2″-*pyridylamino*)-*thiazol*-5′-*yl*]-4-(4′-*pyridyl*)-2(1*H*)-*thiopyrimidine* (*Vc*)

A mixture of 4-methyl-5-[3′-(4″-pyridylacryloyl]-2-(2′-pyridylamino)thiazole (IIc; 3.1 g, 0.01 mol, thiourea (1.52 g, 0.02 mol) and KOH (1.12 g, 0.02 mol) in methanol (50 ml) was refluxed for 5-6 hr, cooled and poured into ice water containing acetic acid (50 ml). The solid obtained was filtered, washed with water and crystallized from ethanol, m.p. 205 . Similarly compounds Va, Vb and Vd were obtained. Their characterization data are given in Table 1.

5-[4′-*Methyl*-2′-(2″-*pyridylamino*)*thiazol*-5′-*yl*]-2-(4′-*pyridyl*)*pyrazoline* (*VIc*)

A mixture of IIc (3.10 g, 0.01 mol), hydrazine hydrate (1 g, 0.02 mol) and acetic acid (20 ml) was heated under reflux for 6 hr, the solid obtained was filtered, washed with water and crystallized from ethanol, m.p. 233 . Compounds VIa, VIb and VId were prepared by a similar procedure and their characterization data are given in Table 1.

3-[4′-*Methyl*-2′-(2″-*pyridylamino*)*thiazol*-5′-*yl*}-5-(3′-*pyridyl*)*isoxazoline* (*VIIb*)

A mixture of 4-methyl-5-[3′-(3″-pyridyl)acryloyl]-2-(2′-pyridylamino)thiazole (IIb; 3.1 g, 0.01 mol), hydroxylamine hydrochloride (1.49 g, 0.02 mol) and KOH (1.12 g, 0.02 mol) in methanol (25 ml) was heated under reflux for 4 hr, cooled and acidified with acetic acid. The solid obtained was filtered, washed with water and crystallized in ethanol, m.p. 228 . The compounds VIIa, VIIc and VIId were similarly prepared and their characterization data are given in Table 1.

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BOOK REVIEWS

Metabolites and Metabolism by Edwin Haslam (Clarenden Press, Oxford), 1985. pp. 161. Price £ 15.00.

This monograph is an addition to already reputed International Series of Monographs on Chemistry.

The book is divided into seven chapters, on the basis of different class of compounds. Each chapter has been further subdivided into sections so as to explain a particular sequence of events. The monograph includes such topics as polyketides and the acetate hypothesis (Chapter 2); alkaloids and nitrogen-containing amino-acid metabolites (Chapter 3); plant phenols (Chapter 4); terpenes and steroids (Chapter 5); some general characteristics of secondary metabolism (Chapter 6); and secondary metabolism-overflow metabolism (Chapter 7).

With everyday improvement in isolation techniques of natural products, aided by fast development of modern physical methods of structure elucidation, introduction of ^{13}C isotopes to study the intact molecules in biosynthetic pathways, indicates that this area of research is bound to advance at a much faster pace.

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This book on the whole is informative and useful to those who are interested in the subject.

Bansi Lal
Research Centre, hoechst India Limited
Mulund, Bombay 400 080

Erratum

Paper entitled "Synthesis of tetrahydropyrido[2,1-*b*]quinazolin-10(1*H*)-one & pentahydroazepino[2,1-*b*]quinazolin-11(1*H*)-one derivatives", *Indian J Chem*, **24B** (1985) 336-337.

On page 337 the title in italics at the beginning of the fourth para should read as *Nitration* and not Nitrogen as printed.

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